PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 48 MAY 2005

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.

Review of the Code and its operation

The ABPI launched a public consultation on the Code and its operation at the end of 2004. The public consultation closed in March by which time a variety of responses had been received. In addition a number of organizations have responded to specific requests. All the responses have been assessed and work is starting on detailed proposals to amend the Code and its operation.

It is anticipated that the new Code will come into operation on 1 January 2006.

Voluntary admissions

Pharmaceutical companies occasionally advise the Authority that they have erroneously used material in breach of the Code.

Such an admission usually relates to a technical matter, such as the omission of the price in prescribing information and action has usually already been taken to correct the breach. In such circumstances, the Authority advises the company that if a complaint were to be received it would have to be considered in the usual way but otherwise no further action is taken.

If a company admits a serious breach of the Code, however, then this information is likely to be used as the basis of a formal complaint against it. Companies are asked to provide details of any action taken to correct the admitted breach and the Director of the Authority then decides whether or not to initiate a formal complaint about the matter.

This accords with advice given by the Code of Practice Appeal Board and published in the Code of Practice Review in August 1997.

Customers' wishes cannot override the Code

When an allegation is made that a company has breached the Code because of arrangements for meetings, for example the provision or offer of inappropriate or excessive hospitality, the company occasionally responds by claiming that it was only so acting at the request of the recipient or recipients.

This contention is unacceptable. Such requests can only be met if this would be in conformity with the requirements of the Code.

The appeal process and fresh allegations

Complainants are reminded that they are not permitted to introduce new allegations, which did not form part of the initial complaint, during the course of an appeal. If a complainant wishes a new allegation to be considered, then a fresh complaint must be made.

Public reprimand for Pfizer

Pfizer Limited has been publicly reprimanded by the ABPI Board of Management for misrepresenting the cardiovascular profile of Celebrex (celecoxib). The ABPI Board was very concerned about this matter, which involved patient safety.

Full details can be found at page 5 of this issue of the Review in the report for Case AUTH/1609/7/04.

House of Commons Health Committee

The Health Committee has published its report on The Influence of the Pharmaceutical Industry and this is available at http://www.publications.parliament.uk/pa/cm/cmhealth.htm.

The Prescription Medicines Code of Practice Authority is currently studying the report and the relevant recommendations will be considered as part of the current review of the Code and its operation.

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.

Forthcoming Code of Practice seminar date on which places remain available is:

Wednesday, 29 June

Friday, 23 September

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 Jean Rollingson for details (020 7930 9677 extn 4).

How to contact the Authority

Our address is:

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Telephone: 020 7930 9677
Facsimile: 020 7930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7930 9677 extn 5).

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.

CASE AUTH/1577/4/04

GENERAL PRACTITIONER v GLAXOSMITHKLINE

Meeting on triptans

A general practitioner complained about an unsolicited facsimile from a market research agency inviting him to take part in a two hour evening group discussion about triptans in the management of migraine. The invitation stated that the incentive was £110.

The complainant was suspicious that this was in fact a promotional meeting and that the payment was in breach of the Code. The agency had told him that it was not a promotional meeting but a standard 'fact-finding' meeting sponsored by a pharmaceutical company; the agency was not at liberty to disclose which one. The complainant had not attended the meeting and so did not know precisely what format it took.

The Authority ascertained from the agency that the meeting had been commissioned by GlaxoSmithKline and the matter was accordingly taken up with that company.

The Panel noted that the invitation stated the name of the market research agency which included the words 'market research'. This was followed by details of the invitees, the name of the sender and the subject 'Triptans in the management of Migraine'. Details of the meeting were given together with 'Incentive: £110'. No mention was made that the meeting was a market research meeting although this might be deduced from the name of the company organising the meeting.

The detailed objectives of the research (which were to be explained at the meeting) were to: understand the effect of triptans (Naramig, Imigran, Zomig and Maxalt) on the management of migraine; evaluate perceptions and image of triptans including differences; look at unmet needs in relation to current therapy and evaluate product development by looking at advertising concepts and proposed story flow for a new presentation of Imigran.

The Panel considered that the invitation was not sufficiently clear that the purpose of the meeting was for market research. The impression that the meeting was a promotional one was compounded by the reference to a financial 'incentive'. High standards had not been maintained. The Panel thus ruled a breach of the Code. It considered that the actual meeting was *bona fide* market research and not disguised promotion. It was acceptable for companies to pay doctors to participate in *bona fide* market research and a payment of £110 for the work involved did not appear to be unreasonable. The Panel ruled no breach of the Code.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure.

A general practitioner complained about an unsolicited facsimile which he had received from a market research agency which invited doctors to take part in an evening group discussion regarding 'Triptans in the management of Migraine'. The meeting would start at 7.15pm finishing at 9.15pm with a buffet/bar available from 7pm. The invitation stated that the incentive was £110.

COMPLAINT

The complainant noted the content of the facsimile and stated that he was suspicious that this was a front for a promotional meeting and that the payment was in breach of the Code. He had contacted the agency and had been told that it was not a promotional meeting but was a standard 'fact-finding' meeting which was sponsored by a pharmaceutical company but that the agency was not at liberty to disclose which one.

The complainant had not accepted the invitation to attend and so did not know precisely what format it took.

The Authority ascertained from the agency that the meeting had been commissioned by GlaxoSmithKline UK Ltd and the matter was accordingly taken up with that company. When writing to GlaxoSmithKline, the Authority asked it to respond in relation to the requirements of Clauses 2, 9.1, 10.1 and 18.1 of the Code.

RESPONSE

GlaxoSmithKline stated that the meeting was one of a series of four meetings organised and run by the market research agency which was commissioned by GlaxoSmithKline to undertake market research on its behalf. The purpose of the research was to provide insight into the management of migraine in primary care, the attitudes of GPs towards prescribing triptans and to test creative storyboard concepts for a potential new campaign. This market research took the form of a 2-hour group discussion led by a facilitator from the agency. Other than the initial brief to the agency GlaxoSmithKline had no role in organising or conducting this meeting, although it did provide the agency with creative storyboard concepts to test as part of the research.

The letter at issue was an initial, speculative letter sent by the agency to 56 GPs in one area in order to gauge the level of interest. Since the market research was to be conducted in a predefined target demographic group, based on the number of years practising as a GP and current triptan usage, this invitation was sent widely in order to reach sufficient numbers of doctors likely to be eligible for participation. However, the number of places for this research meeting was limited to eight. Doctors replying to the speculative letter underwent a telephone screening process to ascertain their eligibility for the market research. This questionnaire was used by the researcher only and was not shown or sent to doctors.

The first eight general practitioners meeting the eligibility criteria and who agreed to participate in the research were sent written confirmation of the arrangements for the meeting. Neither letter encouraged the prescription, supply, sale or administration of either of GlaxoSmithKline's triptans,

Imigran (sumatriptan) or Naramig (naratriptan). Furthermore, neither medicine was named nor claims made for these or any other GlaxoSmithKline medicine in either document. Both letters, along with the meeting that subsequently took place, were entirely non-promotional.

So as not to bias the outcome of the market research it was standard practice to withhold the identity of the commissioning/sponsoring company from participants. Indeed, it was for this reason that the agency was commissioned to act on behalf of GlaxoSmithKline. Therefore, although GlaxoSmithKline's identity as 'sponsor' for the research was not declared on the invitation letter it denied that the letter or the meeting represented a vehicle for disguised promotion or that it had breached Clause 10.1 of the Code.

GlaxoSmithKline referred to current European Pharmaceutical Marketing Research Association (EphMRA) guidance, which was also cited in current British Healthcare Business Intelligence Association (BHBIA) Guidelines which stated: 'Where an interview is conducted with a 'professional' respondent such as a doctor; or with a member of staff of an organisation such as a hospital, it may be necessary and appropriate to recompense that person or organisation for the amount of their working time taken up by the interview. Such incentives or rewards to respondents should be kept to a minimum level, proportionate to the amount of their time involved and should not be more than the normal hourly fee charged by that person for their professional consultancy or advice'.

It was on this basis that the eight participating doctors were each paid £110. Whilst GlaxoSmithKline acknowledged that the language of the speculative letter sent by the market research agency could have been more tactfully worded, the word 'incentive' was a direct quote from the EphMRA and BHBIA Guidelines and had a different meaning to market researchers than it did to doctors. GlaxoSmithKline apologised for any confusion that might have arisen, but confirmed that the meeting was purely for market research. GlaxoSmithKline further confirmed that the fee paid to participants was specifically to compensate doctors for 2 hours of their time spent participating in the market research, and that the fee was in fact below the British Medical Association (BMA) suggested hourly rate. This money was in no way a gift or an inducement to prescribe a GlaxoSmithKline medicine and a breach of Clause 18.1 was denied.

GlaxoSmithKline provided copies of the discussion guide used by the facilitator to conduct the market research. This document was for the facilitator's use only and was not shown to doctors. Also provided were copies of the summary of findings of the research. The company submitted that these documents showed that the meeting represented a genuine piece of market research and not a veiled attempt to promote Imigran or Naramig. GlaxoSmithKline was concerned that a doctor misunderstood the nature of the letter he had received from the market research agency and in light of this complaint it was reviewing procedures for working with agencies to ensure that such invitations would not be misinterpreted in the future. GlaxoSmithKline submitted that the documentation showed that this was a professionally organised market research meeting with sound methodology and objectives; the venue selected and level of hospitality provided was modest. In total £125.55 was spent on food and £50.40 on beverages. GlaxoSmithKline denied that the meeting and its associated arrangements had not maintained high standards and denied a breach of Clause 9.1. Additionally, GlaxoSmithKline denied that it had, either directly or indirectly, brought discredit to the pharmaceutical industry and therefore denied a breach of Clause 2.

PANEL RULING

The Panel noted that the facsimile at issue had been sent by a company carrying out market research on behalf of GlaxoSmithKline. It was an established principle under the Code that pharmaceutical companies were responsible for activities carried out by third parties with their authority. GlaxoSmithKline was thus responsible for the market research activity at issue.

The Panel examined the invitation sent to the complainant. The name of the market research company, which included the words 'Market Research' was given. This was followed by details of the invitees, the name of the sender and the subject 'Triptans in the management of Migraine'. The invitation stated that the meeting would be an evening group discussion. The date, time and location were given together with 'Incentive: £110'.

No mention was made that the meeting was a market research meeting although this might be deduced from the name of the company organising the meeting.

The detailed objectives of the research (which were to be explained at the meeting) were to: understand the effect of 5HT(triptan) therapy on the management of migraine; evaluate perceptions and image of 5HT(triptan) including differences; look at unmet needs in relation to current therapy; and evaluate product development by looking at advertising concepts and proposed story flow. The research focussed on Naramig, Imigran, Zomig and Maxalt. The advertisement concept testing related to a new presentation of Imigran.

The Panel considered that the initial invitation was not sufficiently clear that the purpose of the meeting was for market research. The impression was given that the meeting was a promotional one. The reference to a financial 'incentive' compounded the impression. High standards had not been maintained. The Panel thus ruled a breach of Clause 9.1 of the Code. It considered that the actual meeting was *bona fide* market research and not disguised promotion. It was acceptable for companies to pay doctors to participate in *bona fide* market research and a payment of £110 for the work involved did not appear to be unreasonable. The Panel ruled no breach of Clause 10.1 of the Code and thus no breach of Clause 18.1.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure and ruled accordingly.

Complaint received **22 March 2004**

Case completed **17 June 2004**

CASE AUTH/1609/7/04

MERCK SHARP & DOHME v PFIZER

Celebrex leavepiece

Merck Sharp & Dohme alleged that a Celebrex (celecoxib) leavepiece, entitled 'A COX-2 that keeps the heart in mind', distinguished between the cardiovascular (CV) safety of Celebrex and rofecoxib (Merck Sharp & Dohme's product Vioxx) and promoted Celebrex as a safer selective COX-2 inhibitor in patients at risk of CV disease. Merck Sharp & Dohme was particularly concerned that the leavepiece implied that Celebrex might be prescribed safely to patients at CV risk, whereas such patients were the subject of specific and identical warnings and precautions in the summaries of product characteristics (SPCs) of all selective COX-2 inhibitors.

The Panel noted that although the SPCs for Celebrex and Vioxx were not identical there were similarities. Both products were contraindicated in patients with severe congestive heart failure and both had to be used with caution in patients with, *inter alia*, hypertension.

The Panel considered that the claim 'A COX-2 that keeps the heart in mind' on the front cover of the leavepiece was a broad, unqualified claim about the CV safety of Celebrex. Given the caution expressed in the Celebrex SPC with regard to the product's use in patients with CV problems, the Panel considered that the claim misled as to the CV safety of the product; a breach of the Code was ruled. The Panel did not consider that the claim disparaged rofecoxib as alleged. No breach of the Code was ruled in that regard. These rulings were not appealed.

The heading to page two 'Celebrex. A COX-2 that keeps the heart in mind' was followed by 'Hypertension and arthritis occur as comorbid conditions in at least 40% of OA [osteoarthritis] patients' beneath which text in a highlighted box read 'Patients who are eligible for COX-2 inhibition may therefore commonly have CV risk factors. How would you decide which treatment to use?'. The Panel noted that the remainder of the leavepiece purported to answer that question with sections entitled 'Differences in blood pressure', 'Differences in the risk of CV events' and 'Differences in the risk of MI' concluding with a discussion about CV safety.

The Panel considered that the layout of page two implied that Celebrex was, due to its CV profile, the appropriate treatment for patients who were eligible for COX-2 inhibitors and who might have CV risk factors. A footnote urging caution in patients with CV disease and stating that Celebrex was contraindicated in severe congestive heart failure did not negate the overall impression given. The Panel considered that the claim 'Celebrex. A COX-2 that keeps the heart in mind' and the text at issue in the highlighted box which posed the question 'How would you decide which treatment to use?', within the context of the page were misleading about the CV profile of Celebrex as alleged. A breach of the Code was ruled. This ruling was not appealed.

The Panel noted the final claim on the page 'Celebrex produced a significantly lower mean systolic blood pressure change compared with rofecoxib in elderly hypertensive patients with OA', referenced to Whelton *et al* (2001), appeared beneath the heading 'Differences in blood pressure'. Whelton *et al* compared once daily Celebrex 200mg with Vioxx 25mg in OA patients who were ≥ 65 years of age and already taking antihypertensives. The Panel noted the caution in the Vioxx SPC that, *inter alia*, hypertension with rofecoxib appeared to be dose related and seen with an increased frequency with chronic use and at higher doses. The SPC further stated that in hypertension patients the medicine should be introduced at the lowest recommended dose. Although the Whelton *et al* study lasted only six weeks, and so was not a chronic study, the dose of rofecoxib used, 25mg/day, was the maximum recommended therapeutic dose. The SPC stated that in elderly patients (> 65 years old) the lower dose (12.5mg/day) should be used initially and that care should be exercised when increasing the daily dose from 12.5mg to 25mg. Conversely the dose of Celebrex used by Whelton *et al* was the lowest recommended dose. The Panel thus considered that the doses used in Whelton *et al* represented an unfair comparison of Celebrex and Vioxx and in that regard page 2 of the leavepiece disparaged Vioxx. A breach of the Code was ruled which was upheld on appeal by Pfizer.

The Panel noted Merck Sharp & Dohme had identified two statements on page three 'Differences in the risk of CV events' and 'Differences in the risk of MI'. The first headed a graph adapted from Whelton *et al* (2004) which showed the relative risk of acute MI or stroke in 5,521 patients with OA or rheumatoid arthritis (RA) being treated for hypertension; the relative risks for rofecoxib and Celebrex 2.45 and 1.35 respectively. A box in red to the right of the graph read 'Significant increase in the risk of acute MI or stroke with rofecoxib compared with non-users in treated hypertensive patients with OA or RA'. A green box to the left of the graph read 'No significant difference in the risk of acute MI or stroke in users of Celebrex compared to non-users in treated hypertensive patients with OA or RA'.

The Panel noted that Whelton *et al* (2004) was a retrospective analysis of >3million patients in a healthcare claims database to determine the relative risk of acute MI or stroke associated with, *inter alia*, Celebrex and rofecoxib in treated hypertensive patients with OA and/or RA. The abstract concluded that rofecoxib significantly increased the risk of acute MI or stroke in treated hypertensive patients with OA or RA compared with non-users ($p<0.0001$). Patients receiving celecoxib were at no enhanced risk vs non-users ($p=0.06$ and $p=0.59$ respectively). It was not stated whether the difference between Celebrex and rofecoxib was statistically significant. The confidence intervals for the two medicines overlapped.

The Panel noted that whilst the boxed text adjacent to the graph made it clear that the comparisons were with Celebrex vs non-users and rofecoxib vs non-users the Panel considered that the impression was that the CV safety of rofecoxib and Celebrex had been directly compared and found to be statistically significantly different. No such comparison had been made. The impression of a proven clinically statistically significant difference was reinforced by the heading 'Differences in the risk of CV events' and the subsequent claim which compared Celecoxib with rofecoxib in relation to the risk of MI. The Panel also noted its comments above regarding the CV profile of the medicines as described in their respective SPCs and the footnote 'As with other COX-2 inhibitors and traditional NSAIDS caution should be exercised in patients with cardiovascular disease. Celebrex is contraindicated in severe congestive heart failure'. The Panel considered that the graph on page 3 of the leavepiece represented a misleading and unfair comparison of rofecoxib and celecoxib and in that regard disparaged rofecoxib. Breaches of the Code were ruled which were upheld on appeal by Pfizer.

The subheading 'Differences in the risk of MI' appeared on page 3 above a section which discussed Solomon *et al* (2004) stating that 'within the first 30 days of use, rofecoxib was associated with a 43% greater risk of hospitalisation due to acute MI than Celebrex (p=0.005). This risk persisted up to 90 days of use (p= 0.003)'. The Panel noted that Solomon *et al* was a retrospective observational study among elderly Medicare beneficiaries treated with rofecoxib. Again the Panel noted that the study included patients aged 65 years and over some of whom had taken rofecoxib at doses of greater than 25mg. The Panel noted its comments above and considered that, given the age of the patients and the doses of rofecoxib used, the results of Solomon *et al* did not represent a fair and balanced comparison of rofecoxib and celecoxib and in that regard disparaged rofecoxib as alleged. Breaches of the Code were ruled which were upheld on appeal by Pfizer.

'Celebrex; cardiovascular safety' headed page 4 beneath which a bar chart compared the cardiovascular thrombotic adverse events for Celebrex vs placebo (p=ns) and Celebrex vs NSAIDS (p=ns). The bar chart was adapted from White *et al* (2003), an analysis of 15 controlled arthritis clinical trials for Celebrex (n=31,879). The Panel noted that White *et al* highlighted a number of potential limitations of the meta analysis.

The Panel was extremely concerned that the bar chart implied that there was no statistically significant difference between Celebrex and placebo and NSAIDs in relation to CV thrombotic events. The reader would assume that the CV safety profile of Celebrex was comparable to placebo and that was not so. Given the caution expressed by the study authors the bar chart was not a fair reflection of White *et al*. The Panel noted its comments above regarding CV safety profile of Celebrex as set out in its SPC and the use of footnotes. The Panel considered that the heading 'Celebrex: cardiovascular safety' compounded the overall impression given and was misleading in this regard. A breach of the Code was ruled which was upheld on appeal by Pfizer.

Neither the heading nor the bar chart referred to rofecoxib; the Panel did not consider it disparaged rofecoxib as alleged. No breach of the Code was ruled. This ruling was not appealed.

The Panel noted that the claim on page 5 'Emerging data suggests that there are differences in CV safety between different COX-2 inhibitors' appeared above a section headed 'Clarifying the relative risks of CHD' which described the results of a large retrospective cohort study (n = 378,776). Four bullet points then discussed rofecoxib CV data three of which related to high dose rofecoxib (>25mg) use. The Panel noted that the Vioxx SPC stated that a daily dose of 25mg should not be exceeded in OA; for RA the maximum recommended dose was 25mg and in the elderly care should be exercised when increasing the daily dose from 12.5mg to 25mg. The Panel thus queried the relevance of high dose rofecoxib data to the UK patient population. The Panel was also concerned about the second bullet point 'The risk of serious CHD increased by 70% relative to non-users in the high dose rofecoxib group (p=NS)'; the difference was non-significant and although this had been clearly stated the 70% increase in risk was of such magnitude that a reader might nonetheless attach weight to it despite the fact that it was possibly a chance finding. The Panel noted that the study authors were cautious when describing the risks associated with high dose rofecoxib and noted the study's limitations explaining that patients taking rofecoxib could have differed from non-users of NSAIDs with respect to unmeasured factors that affected the risk of serious CHD. The authors recommended that because patients on high dose rofecoxib had only 13 study events the safety of this dose should be studied further. Ray *et al* (2002) also stated that there was no evidence of raised risk of CHD among users of rofecoxib at doses of 25mg or less. This was reflected in the final bullet point on the page in question.

The Panel noted that the supplementary information to Clause 7.2 stated that particular care must be taken to ensure that issues of 'emerging clinical or scientific opinion' were treated in a balanced manner in promotional material. The Panel considered that the layout of the page was such that a reader would assume that emerging data suggesting differences in CV safety between different COX-2 inhibitors was in part explained and clarified by the bullet points set out beneath the heading 'Clarifying the relative risks of CHD'. The majority of bullet points however referred to an unlicensed, high dose of Vioxx. The Panel again noted its comments above and considered that page 5 represented an unfair criticism of Vioxx and was thus misleading. A breach of the Code was ruled. The Panel also considered that Vioxx had been disparaged. A further breach of the Code was ruled which was upheld on appeal by Pfizer.

During its consideration of this case the Panel was extremely concerned that the leavepiece implied that

there was no need to worry about the CV tolerability profile of Celebrex. This was not so. In the Panel's view the leavepiece was such that patient safety could be compromised. This was a serious matter. The Panel considered that had an allegation of a breach of Clause 2 been made it would have ruled a breach of that clause as a sign of particular censure. The Panel decided to report Pfizer to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board was extremely concerned that the leavepiece implied that there was no need to worry about the CV tolerability profile of Celebrex. This was not so. The Celebrex SPC advised caution in patients with a history of a number of CV problems and was contraindicated in severe CHF. A barchart in the leavepiece implied that there was no statistically significant difference between the CV safety of Celebrex and placebo. In the Appeal Board's view the leavepiece was such that patient safety in relation to the use of Celebrex could be compromised. This was a serious matter. The Appeal Board decided to require Pfizer to take steps to recover the leavepiece as set out in Paragraph 10.3 of the Constitution and Procedure. Pfizer should write as soon as possible to each health professional to whom the leavepiece had been detailed to give details of the case and to request, where practicable, return of the leavepiece.

Further, the Appeal Board decided that the matter should be reported to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure. The Appeal Board considered that it would have required Pfizer to issue a corrective statement if it had the power to do so. The Appeal Board therefore recommended that the ABPI Board consider such an option.

The ABPI Board noted that Pfizer had been required to recover the leavepiece. The letter had been agreed with the Authority. The ABPI Board was concerned that the letter did not give the impression that Pfizer agreed with the rulings. The ABPI Board noted Pfizer's submission that the European Medicines Evaluation Agency (EMEA) and the Food & Drug Administration (FDA) were reviewing Celebrex data with a report expected later in February. The ABPI Board considered that taking all the circumstances into account the publication of a corrective statement could cause confusion amongst health professionals. The ABPI Board, however, was very concerned about this matter which involved patient safety and decided that Pfizer should be publicly reprimanded.

Merck Sharp & Dohme Limited complained about a six page gate-folded leavepiece (ref CEL 1133) for Celebrex (celecoxib) issued by Pfizer Limited entitled 'A COX-2 that keeps the heart in mind' which compared the cardiovascular (CV) tolerability of Celebrex with, *inter alia*, Merck Sharp & Dohme's product Vioxx (rofecoxib) in relation to blood pressure, risk of CV events, risk of myocardial infarction and cardiovascular safety.

Both Celebrex and rofecoxib were selective cyclo-oxygenase 2 (COX-2) inhibitors and each was indicated for symptomatic relief in the treatment of osteoarthritis (OA) or rheumatoid arthritis (RA).

COMPLAINT

Merck Sharp & Dohme alleged that the leavepiece distinguished between the CV safety of Celebrex and rofecoxib and promoted Celebrex as a safer selective COX-2 inhibitor in patients at risk of cardiovascular disease. From a patient and a prescriber's perspective, Merck Sharp & Dohme was particularly concerned that the leavepiece implied that Celebrex might be prescribed safely to patients at cardiovascular risk, whereas such patients were the subject of specific and identical warnings and precautions in the summaries of product characteristics (SPCs) of all selective COX-2 inhibitors.

Merck Sharp & Dohme did not consider that Pfizer could claim clinically meaningful differences between the products based on CV safety and alleged that the following statements were misleading and disparaged rofecoxib, in breach of Clauses 7.2 and 8.1 of the Code: 'A COX-2 that keeps the heart in mind … Celebrex celecoxib' (Page 1); 'Celebrex A COX-2 that keeps the heart in mind', '… Patients …eligible for COX-2 inhibition may therefore commonly have CV risk factors. How would you decide which treatment to use?' (Page 2); 'Differences in the risk of CV events', 'Differences in the risk of MI' (Page 3); 'Celebrex: cardiovascular safety' (Page 4) and 'Are all COX-2's [sic] equal?', 'Emerging data suggests that there are differences in CV safety between different COX-2 inhibitors' (Page 5).

Merck Sharp & Dohme explained that selective COX-2 inhibitors had recently been reviewed by the Committee for Proprietary Medicinal Products (CPMP), at the request of the French government, and as a result the SPCs of the entire class of medicines, including those for Celebrex and rofecoxib, were harmonised in a number of important areas. For example, the SPC wording about CV tolerability was now identical for both products.

The SPC for Celebrex (and for rofecoxib) stated in Section 4.4:

'COX-2 selective inhibitors are not a substitute for acetylsalicylic acid for the prophylaxis cardiovascular thromboembolic diseases because of their lack of effect on platelets function. Because celecoxib [rofecoxib] does not inhibit platelet aggregation, antiplatelet therapies (e.g. acetylsalicylic acid) should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular and other thrombotic events (prior history of MI, angina, ischemic heart disease, atherosclerotic heart disease, CVA, cerebral ischemia, coronary by pass graft surgery or peripheral vascular surgery) (see 4.5 and 5.1)'

and

'Caution should be exercised in patients with a medical history of ischemic heart disease because of the pharmacodynamic profile of COX-2 selective inhibitors noted above. Appropriate measures should be taken and discontinuation of celecoxib [rofecoxib] therapy should be considered if there is clinical

evidence of deterioration in the condition of specific clinical symptoms in these patients'.

In addition (non-harmonised but identical wording), Section 4.4 also stated:

'… celecoxib [rofecoxib] should be used with caution in patients with a history of cardiac failure, left ventricular function or hypertension, and in patients with pre-existing oedema ...'.

Merck Sharp & Dohme considered that the leavepiece at issue suggested that there were clinically meaningful differences between Celebrex and rofecoxib in terms of CV safety, which were not borne out by the CPMP review of the class.

Merck Sharp & Dohme noted that Pfizer had based its claim of differences in CV safety on retrospective data derived from the databases of pharmaceutical benefits programmes in the United States. The prime purpose of such databases was patient management and billing. Safety studies derived from these databases needed to be interpreted with caution as they were subject to bias and confounding. Investigators did their best to reduce such biases but one could not be confident that the groups being studied had the same baseline risk, and it was widely accepted that the use of such data was to generate and not to test a hypothesis; results would never be definitive. The only way one could confidently make claims on CV safety was through an adequately powered prospective randomised study. Merck Sharp & Dohme knew of no study either underway or completed comparing Celebrex with rofecoxib with major cardiovascular events as endpoints, although Weir *et al* (2003) had examined the rofecoxib randomised controlled clinical trial database for cardiovascular thrombotic events. Their pooled analysis of 23 studies encompassing multiple disease states and including more than 14,000 patient-years at risk demonstrated that rofecoxib was not associated with excess CV thrombotic events compared with either placebo or non-naproxen NSAIDs. (Naproxen appeared to be the outlier, suggesting a cardioprotective benefit of naproxen).

In addition, with regard to page 5 of the leavepiece, Merck Sharp & Dohme understood that the CPMP required pharmaceutical companies to provide copies of all the relevant data and consequently it seemed improbable that significant relevant data could have become available that were not available to the CPMP before it published its review. Merck Sharp Dohme could not see therefore how the data quoted in the leavepiece could be characterised as 'emerging data' which superseded the results of the CPMP's review.

The overall impression of the leavepiece was that Celebrex was a safe medicine in patients at cardiovascular risk. On a number of pages, there were some small print footnotes pointing to the CV precautions for Celebrex listed in the SPC (there was no such warning on the front cover). The consistent view of the Authority had been, however, that an otherwise misleading claim could not be rendered acceptable by the use of footnotes. Accordingly the inclusion of the footnotes did not prevent the leavepiece being misleading.

The front cover headline 'A COX-2 that keeps the heart in mind' was a gross oversimplification which was clearly intended to convey a safety message in contradiction of the SPC; it was thus misleading in its own right as well as setting the tone and directing the perception of the leavepiece as previously noted – safe to use in patients at CV risk. The leavepiece therefore completely disregarded the fact that the CPMP determined that the same harmonised warning be inserted into the SPCs for all selective COX-2 inhibitors. The CPMP reviewed all the data contained in this piece in its review of the class. There was no suggestion that Celebrex was a 'safer' COX-2 inhibitor compared with other members of the class, either in the CPMP review or in the SPC as amended following the CPMP review.

Merck Sharp & Dohme had been told by Pfizer that it intended to remove the leavepiece in about 4 weeks 'with a view to changing its content and context'. It seemed likely that the leavepiece would receive intensive use until then.

RESPONSE

Pfizer explained that it had produced the leavepiece to support the CV profile of Celebrex in the light of scientific publications and articles in the health press which raised concerns over the CV effects of COX-2 specific inhibitors. Pfizer provided a copy of one article from GP (31 May 2004) entitled 'Celecoxib 'safer' for elderly use' which discussed Mamdani *et al* (2003) together with a copy of the 'Synovium' newsletter produced by the Working Group on Primary Care Postgraduate Education of the Arthritis Research Campaign (ARC). On the bottom right hand corner of the front page of the newsletter there was boxed text entitled 'A Word of Warning'. This box contained the following comment relating to Solomon *et al* (2004): 'Another study has reported an increased incidence of acute myocardial infarction in patients treated with rofecoxib. GPs should now think very carefully before prescribing this drug in their osteoarthritic patients, especially those with cardiac risk factors. It might be a good idea to run a search on your practice database to see if patients currently being prescribed rofecoxib have any cardiac risk factors'.

Pfizer considered these articles highlighted the relevance of the CV safety of COX-2s to clinicians, and therefore the rationale for Pfizer providing this information to them.

Pfizer explained that the leavepiece was used as part of a more general cardiovascular orientated discussion, to help communicate to GPs who already prescribed COX-2s that osteoarthritis and CV disease (hypertension) commonly occurred as co-morbid conditions; Celebrex had been shown to have a similar CV safety profile to non-specific NSAIDs; there were differences between COX-2s with respect to CV effects.

Pfizer did not accept that the leavepiece implied that Celebrex was safe to prescribe in any particular patient group. However, as noted above, an aim of the leavepiece was to highlight some differences in the CV side effect profiles of the COX-2s, which could

be of particular importance to prescribers (and therefore patients) given the frequency with which these diseases occurred as co-morbid conditions. Pfizer did not consider that it was claiming anything other than what the data presented in the leavepiece suggested. In including studies by Mamdani *et al* and Ray *et al* (2002), Pfizer considered that it had provided balancing data in support of the CV safety of rofecoxib as well as Celebrex as compared with traditional NSAIDs or non-users. It did not therefore consider that it had breached Clauses 7.2 and 8.1 of the Code. In considering clinically significant outcomes, it was important to point out that prospective studies by Whelton *et al* (2001) and Whelton *et al* (2002) had shown that rofecoxib raised the average systolic blood pressure of elderly OA patients by up to 3mmHg. Whelton *et al* (2001) also commented that relatively small changes in blood pressure could have profound public health implications and that a sustained increase in systolic blood pressure of 3mmHg could explain a 10% to 20% increase in congestive heart failure, a 15% to 20% increase in stroke risk and a 12% increase in angina risk.

Pfizer agreed that the paragraphs from the Celebrex SPC listed in the complaint were identical in the Vioxx SPC. However, Merck Sharp & Dohme had omitted significant portions of text and beginnings of sentences and therefore these segments did not accurately reflect the individual SPCs and as such did not highlight some highly important differences between them.

Section 4.4 of the Celebrex SPC stated that 'As with other drugs known to inhibit prostaglandin synthesis fluid retention and oedema have been observed in patients taking Celecoxib'.

Section 4.4 of the Vioxx SPC stated that 'Fluid retention, oedema and hypertension have been observed in patients taking rofecoxib. These effects appear to be dose related and are seen with an increased frequency with chronic use of rofecoxib and at higher doses. The reporting rates for hypertension with rofecoxib have been similar to or, on occasion, slightly greater than some other NSAIDs, at comparable doses'.

In addition, Section 4.8 of the Vioxx SPC listed hypertension as a common undesirable effect, whilst in the corresponding section of the Celebrex SPC, hypertension was listed as an uncommon effect.

These differences in the occurrence and incidence of hypertension were reflected by the results of the two prospective, randomised, controlled trials by Whelton *et al* in hypertensive elderly osteoarthritis patients. Building on these data and differences between the SPCs the leavepiece presented some retrospective studies that showed differences in CV outcomes when comparing Celebrex or rofecoxib with non-specific NSAIDs, or non-users or when comparing Celebrex and rofecoxib. Some of these data were not available to the CPMP to consider as part of its review of the class as they were published too late to be included. Irrespective of whether the data were available to the CPMP for review, the clinical studies were of high quality, most appearing in premier, peer reviewed journals and all had important results that progressed understanding of these medicines.

Pfizer strongly disagreed with the criticism that the leavepiece was intended to suggest that there were differences between Celebrex and rofecoxib. The leavepiece was primarily intended to support the CV safety profile of Celebrex vs NSAIDs, whilst other comparisons were also made versus rofecoxib and non-users and as such some points did not even mention rofecoxib whilst others showed equivalence between Celebrex, rofecoxib and non-users.

Whelton *et al* (2001) which pointed out the differential effect of Celebrex and rofecoxib on blood pressure, was a prospective randomised controlled trial (RCT). Pfizer acknowledged that, in terms of hierarchy of data, RCTs were preferable to observational studies. However, RCTs were not always suitable to comment on safety due to the relative infrequency of some adverse events eg cardiovascular endpoints such as MI. In addition, in the absence of RCT data, high quality observational data could not be ignored, especially in the light of the numbers of such studies available and the large patient numbers involved. The leavepiece clearly labelled all such studies that suggested differences between Celebrex and rofecoxib, as retrospective, so as not to mislead the reader.

Pfizer did not disagree with any of the findings of the pooled analysis by Weir *et al* (2003). However, it reiterated that prospective RCTs were not always suitable to point out safety differences between medicines due to the relative infrequency of some adverse events. In addition, it was not clear whether all the trials included in the analysis were prospectively designed to provide CV outcome data. Only trials lasting ≥ 4 weeks were included and some trials were in patient groups not covered by the therapeutic indications of rofecoxib (Alzheimer's disease and chronic low back pain). With regard to the comment in Merck Sharp & Dohme's complaint suggesting a cardio-protective benefit of naproxen, Pfizer considered that it was important to point out that the issue regarding whether naproxen might be cardio-protective or not was ambiguous and studies investigating this area had arrived at conflicting conclusions. Some case control studies had demonstrated that naproxen might have some mild cardio-protective effect in various groups of patients. In contrast however, other case control/observational studies had failed to find such an association. Additionally an analysis of 15 controlled arthritis clinical trials for Celebrex failed to show a significant difference in the incidence of cardiovascular Antiplatelet Trialist Collaboration end points (APTC) between Celebrex and naproxen.

Pfizer stated that Ray *et al* (2002) was available to the CPMP but at the time of its review it decided not to include any retrospective data in the labels for the COX-2 selective medicines. However, the leavepiece presented studies, Whelton *et al* and Solomon *et al*, which, as they were published in March 2004 and May 2004 respectively, would qualify as emerging data. Both studies were published too late for consideration by the CPMP.

As mentioned above, irrespective of whether these data were reviewed by the CPMP or not the data represented high-quality research, the findings of which, were important to prescribers.

It was not Pfizer's aim to suggest Celebrex was safe in any patient group and it did not consider that the leavepiece gave this impression. The information reflecting the SPC, which was printed on all pages except the front cover, was inserted to provide an extra level of clarification with respect to the use of Celebrex in this patient group.

The headline 'A COX-2 that keeps the heart in mind' was not intended to, nor did it, suggest an inappropriate safety message for Celebrex. This particular line was chosen to highlight, to the prescriber, that they should 'keep in mind' cardiovascular safety for their patients no matter what illness they might be treating at the time. Prescribers could compartmentalise different illnesses and therefore the headline was intended to be used as a bridge to open discussion about co-morbidity of hypertension and osteoarthritis.

The leavepiece existed within the scope of the SPC for Celebrex and acknowledged the warnings, regarding CV disease, inserted into it by the CPMP. As far as Pfizer was aware, due to the timelines of publication and finalisation of the referral process (described above) the CPMP could not have viewed all the data contained within the leavepiece. Had all the data been available at the time of referral, it could only speculate as to whether it would have had an impact on the SPCs, in the light of their size and agreement on the relative comparable safety of Celebrex, rofecoxib and NSAIDs. The current SPCs did not contain any reference to retrospective data at this point in time.

Pfizer submitted that there were important differences between the SPCs for Celebrex and Vioxx, which were highlighted in the leavepiece and outlined above. Furthermore data published by Mamdani *et al*, in the last few months, which was not included in the CPMP referral or the leavepiece had reinforced the position that there were differences, in the CV adverse event profile, between Celebrex and rofecoxib. Due to the wealth of these retrospectively gained data, giving an apparently consistent message of Celebrex's similarity to NSAIDs and of a differentiation between Celebrex and rofecoxib, Pfizer continued to feel comfortable in presenting these data.

Based on the differences between the Celebrex and Vioxx SPCs, the relevant prospective randomised controlled trials and the balance of retrospective studies presented in the Celebrex leavepiece Pfizer considered Celebrex had a similar CV safety profile to non-specific NSAIDs; there were differences, between Celebrex and rofecoxib, in their effects on the cardiovascular system and on the occurrence of CV adverse events in certain patient populations exposed to each of these medicines.

In presenting the data Pfizer had paid a great deal of attention and taken great care to ensure that all the points which had been made were balanced, fair, objective and unambiguous, were based on an up-to-date evaluation of all evidence, reflected that evidence clearly and did not mislead either directly or by implication. In addition, Pfizer had tried to ensure that they were not biased and were as balanced as possible. Under these circumstances Pfizer did not believe it had breached Clauses 7.2 and 8.1 of the Code.

PANEL RULING

The Panel noted that although the SPCs for Celebrex and Vioxx were not identical there were similarities. Both products were contraindicated in patients with severe congestive heart failure. With regard to special precautions and warnings for use (Section 4.4) both SPCs noted that COX-2 selective inhibitors were not a substitute for aspirin for prophylaxis of cardiovascular thrombo-embolic diseases. Prescribers were therefore urged to exercise caution if using either Celebrex or Vioxx in patients with a history of ischaemic heart disease.

The Celebrex SPC stated that as with other medicines known to inhibit prostaglandin synthesis fluid retention and oedema had been observed in patients taking celecoxib and therefore caution was urged in patients with cardiac failure, left ventricular dysfunction or hypertension and in patients with pre-existing oedema from any other reason. It was further stated that compromised renal or hepatic function and especially cardiac dysfunction were more likely in the elderly in whom the lowest effective dose should be used and therefore medically appropriate supervision should be maintained.

The Vioxx SPC stated that fluid retention, oedema and hypertension had been observed and these effects appeared to be dose related and seen with an increased frequency with chronic use and at higher therapeutic doses. The reporting rates for hypertension had been similar to or on occasion slightly greater than for some other NSAIDS at comparable doses. Because Vioxx might result in fluid retention caution was advised in patients with a history of cardiac failure, left ventricular dysfunction or hypertension and in patients with pre-existing oedema from any other reason. The Vioxx SPC stated that medically appropriate supervision should be maintained when using Vioxx in the elderly and in patients with renal, hepatic or cardiac dysfunction.

With regard to undesirable effects the Celebrex SPC listed palpitations and hypertension as uncommon events (≥ 1/1000, < 1/100) and stated that there had been very rare or isolated reports (< 1/10,000) of congestive heart failure, heart failure and myocardial infarction. Hypertension was listed as a common (≥ 1/100; < 1/10) effect in the Vioxx SPC, congestive heart failure occurred rarely (≥ 1/10,000, < 1/1000) and there had been very rare or isolated reports of myocardial infarction, pulmonary oedema, palpitations, cerebral vascular accident, hypertensive crisis and vasculitis.

The Panel considered that the claim 'A COX-2 that keeps the heart in mind' on the front cover of the leavepiece was a broad, unqualified claim about the cardiovascular safety of Celebrex. Given the caution expressed in the Celebrex SPC, the Panel considered that the claim at issue gave a misleading impression

about the cardiovascular safety of the product; a breach of Clause 7.2 was ruled. The Panel did not consider the claim was a direct or implied comparison and thus did not consider that it disparaged rofecoxib as alleged. No breach of Clause 8.1 was ruled. These rulings were not appealed.

The Panel noted the heading to page two 'Celebrex. A COX-2 that keeps the heart in mind' was followed by 'Hypertension and arthritis occur as comorbid conditions in at least 40% of OA patients' beneath which text in a highlighted box read 'Patients who are eligible for COX-2 inhibition may therefore commonly have CV risk factors. How would you decide which treatment to use?'. The Panel noted that the remainder of the leavepiece purported to answer that question with sections entitled 'Differences in blood pressure', 'Differences in the risk of CV events' and 'Differences in the risk of MI' concluding with a discussion about cardiovascular safety.

The Panel considered that the layout of page two implied that 'Celebrex. A COX-2 that keeps the heart in mind' was, due to its cardiovascular profile, the appropriate treatment for those patients described in the highlighted box who were eligible for COX-2 inhibitors and who might have CV risk factors. The Panel noted the cardiovascular profile of Celebrex as set out in its SPC and its comment and ruling on the closely similar claim on the front cover. A footnote at the bottom of pages 2, 3, 4 and 5 which read 'As with other COX-2 inhibitors and traditional NSAIDs caution should be exercised in patients with cardiovascular disease. Celebrex is contraindicated in severe congestive heart failure' did not negate the overall impression given. In any event the Panel noted that it was an established principle under the Code that otherwise misleading claims could not be qualified by footnotes or small print. The Panel considered that the claim 'Celebrex. A COX-2 that keeps the heart in mind' and the text at issue in the highlighted box which posed the question 'How would you decide which treatment to use?', within the context of the page were misleading about the CV profile of Celebrex as alleged. A breach of Clause 7.2 was ruled. This ruling was not appealed by Pfizer.

The Panel noted that whilst the claim and text at issue did not mention rofecoxib it was mentioned in the final claim on the page 'Celebrex produced a significantly lower mean systolic blood pressure change compared with rofecoxib in elderly hypertensive patients with OA' referenced to Whelton *et al* (2001) which appeared beneath the heading 'Differences in blood pressure'. Whelton *et al* (2001) compared once daily Celebrex 200mg with Vioxx 25mg in OA patients who were ≥ 65 years of age and already taking antihypertensives. The Panel noted the caution in the Vioxx SPC that fluid retention, oedema and hypertension with rofecoxib appeared to be dose related and seen with an increased frequency with chronic use of rofecoxib and at higher therapeutic doses. The SPC further stated that because Vioxx might result in fluid retention, caution should be exercised in patients with, *inter alia*, hypertension and the medicine introduced at the lowest recommended dose in these patients. Although the Whelton *et al* study lasted only six weeks, and so was not a chronic study, the dose of rofecoxib used, 25mg/day, was the maximum recommended therapeutic dose. The SPC stated that in elderly patients (> 65 years old) the lower dose (12.5mg/day) should be used initially and that care should be exercised when increasing the daily dose from 12.5mg to 25mg. Conversely the dose of Celebrex used by Whelton *et al* was the lowest recommended dose. The Panel thus considered that the doses used in Whelton *et al* represented an unfair comparison of Celebrex and Vioxx and in that regard page 2 of the leavepiece disparaged Vioxx. A breach of Clause 8.1 was ruled. This ruling was appealed by Pfizer.

The Panel noted Merck Sharp & Dohme had identified two statements on page three 'Differences in the risk of CV events' and 'Differences in the risk of MI'. The first headed a graph adapted from Whelton *et al* (2004) which showed the relative risk of acute MI or stroke in 5,521 patients with OA or RA being treated for hypertension; the relative risks were rofecoxib 2.45, Celebrex 1.35, NSAID 1.11 and a non-NSAID 1.0. A box in red to the right of the graph read 'Significant increase in the risk of acute MI or stroke with rofecoxib compared with non-users in treated hypertensive patients with OA or RA'. A green box to the left of the graph read 'No significant difference in the risk of acute MI or stroke in users of Celebrex compared to non-users in treated hypertensive patients with OA or RA.

The Panel noted that Whelton *et al* (2004), published as an abstract, was a retrospective analysis of >3million patients in a healthcare claims database to determine the relative risk of acute MI or stroke associated with Celecoxib, rofecoxib and non specific NSAIDs in treated hypertensive patients with OA and/or RA. The abstract concluded that rofecoxib significantly increased the risk of acute MI or stroke in treated hypertensive patients with OA or RA compared with non-users ($p<0.0001$). Patients receiving, *inter alia*, celecoxib and non specific NSAIDs were at no enhanced risk vs non-users ($p=0.06$ and $p=0.59$ respectively). Limited data was provided in the abstract; it was not stated whether the difference between Celecoxib and rofecoxib was statistically significant. The confidence intervals for the two medicines overlapped. The Panel noted that Whelton *et al* (2004) gave no information about the doses used. A footnote to the graph stated 'Doses of treatment not specified in this abstract'. The Panel noted the Vioxx SPC stated that 'Fluid retention, oedema and hypertension … appear to be dose related …. Because treatment with rofecoxib may result in fluid retention, caution should be exercised in patients with … hypertension and in patients with pre-existing oedema from any other reason. Rofecoxib should be introduced at the lowest recommended dose in those patients'.

The Panel noted that whilst the boxed text adjacent to the graph made it clear that the comparisons were with Celebrex vs non-users and rofecoxib vs non-users the Panel considered that the impression was that the CV safety of rofecoxib and Celebrex had been directly compared and found to be statistically significantly different. No such comparison had been made. The impression of a proven clinically

statistically significant difference was reinforced by the heading 'Differences in the risk of CV events' and the subsequent claim which compared Celecoxib with rofecoxib in relation to the risk of MI.

The Panel noted Merck Sharp & Dohme's submission that there was no prospectively designed trial wherein the CV safety of the two had been directly compared. Whilst it was made clear that the data was a retrospective cohort analysis it was not made clear that the data derived from an American healthcare claims database. The Panel also noted its comments above regarding the CV profile of the medicines as described in their respective SPCs and the footnote 'As with other COX-2 inhibitors and traditional NSAIDS caution should be exercised in patients with cardiovascular disease. Celebrex is contraindicated in severe congestive heart failure'. The Panel considered that the graph on page 3 of the leavepiece represented a misleading and unfair comparison of rofecoxib and celecoxib and in that regard disparaged rofecoxib. Breaches of Clauses 7.2 and 8.1 were ruled. These rulings were appealed by Pfizer.

The subheading 'Differences in the risk of MI' appeared on page 3 above a section which discussed Solomon *et al* (2004) stating that 'within the first 30 days of use, rofecoxib was associated with a 43% greater risk of hospitalisation due to acute MI than Celebrex (p=0.005). This risk persisted up to 90 days of use (p= 0.003)'. An adjacent pie chart was used to illustrate 43%. The Panel noted that Solomon *et al* was a retrospective observational study which showed an elevated risk of hospitalisation for acute MI among elderly Medicare beneficiaries treated with rofecoxib. Again the Panel noted that the study included patients aged 65 years and over some of whom had taken rofecoxib at doses of greater than 25mg. The Panel noted its comments above with regard to fluid retention, hypertension and the recommended dose in the elderly. The Panel considered that, given the age of the patients and the doses of rofecoxib used, the results of Solomon *et al* did not represent a fair and balanced comparison of rofecoxib and celecoxib and in that regard disparaged rofecoxib as alleged. Breaches of Clauses 7.2 and 8.1 were ruled. These rulings were appealed by Pfizer.

'Celebrex; cardiovascular safety' headed page four beneath which a bar chart compared the cardiovascular thrombotic adverse events (Antiplatelet Trialist's Collaboration (APTC) endpoints) for all patients whether or not they were taking aspirin. The results shown were Celebrex vs placebo (p=ns) and Celebrex vs NSAIDS (p=ns). The bar chart was adapted from White *et al* (2003) which was described as an analysis of 15 controlled arthritis clinical trials for Celebrex (n=31,879). The Panel noted that White *et al* highlighted potential limitations of the meta analysis; the studies utilized for the analysis were not originally designed to assess the relative effects of Celebrex on cardiovascular events although the baseline CV risk factors and use of aspirin were comparable amongst treatment groups. Another potential concern was sample size, event numbers and patient years of follow-up for the placebo and naproxen groups was relatively small and so the description of absolute risk relative to placebo must be interpreted with caution. Thus although the most confident interpretation of these data related to comparison with NSAIDs, the total number of events included in the study was relatively modest and occurred primarily in trials geared toward the development of a database for drug approval and gastrointestinal safety assessment; the power to detect true relative risks in the 1.2 to 1.4 range associated with harm was not high. This potential deficit was compensated in part by the availability and use of original source data for CV events which would be expected to add to the credibility of the results.

The Panel was extremely concerned that the bar chart gave the impression that there was no statistically significant difference between Celebrex and placebo and NSAIDs in relation to CV thrombotic events. The reader would gain the impression that the CV safety profile of Celebrex was comparable to placebo and that was not so. Given the caution expressed by the study authors the bar chart was not a fair reflection of White *et al*. The Panel noted its comments above regarding CV safety profile of Celebrex as set out in its SPC and the footnote 'As with other COX-2 inhibitors and traditional NSAIDs caution should be exercised in patients with cardiovascular disease. Celebrex is contraindicated in severe congestive heart failure'. The Panel considered that the heading 'Celebrex: cardiovascular safety' compounded the overall impression given and was misleading in this regard. A breach of Clause 7.2 was ruled. This ruling was appealed by Pfizer.

Neither the heading nor the bar chart referred to rofecoxib; the Panel did not consider it disparaged rofecoxib as alleged. No breach of Clause 8.1 was ruled.

The Panel noted that the claim on page 5 'Emerging data suggests that there are differences in CV safety between different COX-2 inhibitors' appeared above a section headed 'Clarifying the relative risks of CHD' which described the results of a large retrospective cohort study of 378,776 individuals. Four bullet points then discussed rofecoxib CV data referenced to Ray *et al* (2002). The leavepiece stated (by means of an asterisk and a footnote) that in Ray *et al* CHD was defined as 'hospital admission for acute MI or death from CHD.

The Panel noted that three of the bullet points related to high dose rofecoxib (>25mg) use. The Panel noted that the Vioxx SPC stated that a daily dose of 25mg should not be exceeded in OA; for RA the maximum recommended dose was 25mg and in the elderly care should be exercised when increasing the daily dose from 12.5mg to 25mg. The Panel thus queried the relevance of high dose rofecoxib data to the UK patient population. The Panel was also concerned about the second bullet point 'The risk of serious CHD increased by 70% relative to non-users in the high dose rofecoxib group (p=NS)'; the difference was non-significant and although this had been clearly stated the 70% increase in risk was of such magnitude that a reader might nonetheless attach weight to it despite the fact that it was possibly a chance finding. The Panel noted that the study authors used cautious language when describing the risks associated with high dose rofecoxib; 'our results **indicate** that high-

dose rofecoxib **could** be **associated** with a raised risk of serious CHD …' (emphasis added). The study authors noted its limitations explaining that patients taking rofecoxib could have differed from non-users of NSAIDs with respect to unmeasured factors that affected the risk of serious CHD. The authors recommended that because patients on high dose rofecoxib had only 13 study events, further monitoring of the safety of this dose should be done. Ray *et al* also stated that there was no evidence of raised risk of CHD among users of rofecoxib at doses of 25mg or less. This was reflected in the final bullet point on the page in question.

The Panel noted that the supplementary information to Clause 7.2 'emerging clinical or scientific opinion' required that with such issues particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. The Panel considered that the layout of the page was such a reader would assume that emerging data suggesting differences in CV safety between different COX-2 inhibitors was in part explained and clarified by the bullet points set out beneath the heading 'Clarifying the relative risks of CHD'. The majority of bullet points however referred to an unlicensed, high dose of Vioxx. The Panel again noted its comments above with regard to fluid retention, hypertension and recommended doses. The Panel considered that page 5 represented an unfair criticism of Vioxx and was thus misleading and disparaging as alleged. Breaches of Clauses 7.2 and 8.1 were ruled. Pfizer accepted the ruling of a breach of Clause 7.2 but appealed the Panel's ruling of a breach of Clause 8.1.

During its consideration of this case the Panel was extremely concerned that the leavepiece gave the impression that there was no need to worry about the cardiovascular tolerability profile of Celebrex. This was not so. The Celebrex SPC advised caution in patients with a history of ischaemic heart disease, cardiac failure, left ventricular dysfunction or hypertension. Appropriate medical supervision must be maintained especially in the elderly. The bar chart on page 4 of the leavepiece implied that there was no statistically significant difference between the cardiovascular safety of Celebrex and placebo. In the Panel's view the leavepiece was such that patient safety could be compromised. This was a serious matter. The Panel considered that had an allegation of a breach of Clause 2 been made it would have ruled a breach of that clause as a sign of particular censure. The Panel decided to report Pfizer to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

APPEAL BY PFIZER

Pfizer stated that the leavepiece in question had been withdrawn after internal review and following its acceptance of some of the Panel's rulings of breaches of the Code. In the light of the global withdrawal of Vioxx for all doses in all indications, all Celebrex materials containing references to rofecoxib were being reviewed.

Pfizer submitted that the Panel had not fully appreciated the very important differences between the SPCs for Vioxx and Celebrex in the wording of both special warnings (Section 4.4) and the undesirable effects (Section 4.8). Pfizer submitted that due to the inclusion of 'hypertension' in Section 4.4 of the rofecoxib SPC (as an outcome) but not in that of Celebrex, and the fact that hypertension and congestive heart failure (CHF) were listed as occurring respectively an order of magnitude (ten times) more commonly with rofecoxib than Celebrex that, based on the SPCs, the CV profile of Celebrex was not the same as the CV profile of rofecoxib. The Panel's and Merck Sharp & Dohme's basic assumption that both SPCs were the same was clearly incorrect and an oversimplification. Available trial data largely signalled an inferior cardiovascular profile for Vioxx compared to traditional NSAIDs and Celebrex. The subsequent withdrawal of Vioxx by Merck Sharp & Dohme, with no advanced warning to health professionals bore this out.

Pfizer submitted that its use of Whelton *et al* (2001) regarding the comparison between 200mg Celebrex and 25mg Vioxx was valid. Market data for June 2004 for OA and RA prescriptions showed that prescriptions for the month for Celebrex 100mg were 3537, and for Celebrex 200mg were 6504 (hence 65% of the Celebrex prescriptions for OA or RA were at 200mg). Similarly for Vioxx from the June data, prescriptions for Vioxx 12.5mg were 4477, and for Vioxx 25mg were 4610 (hence 51% of prescriptions for Vioxx for OA or RA were at 25mg). Therefore there was significant usage of 25mg of Vioxx in the OA and RA population (DIN-LINK data, MAT June 2004). Presentation of these data were very relevant to health professionals. The vast majority of patients receiving Celebrex or rofecoxib were over 65 years as per the National Institute of Clinical Excellence (NICE) guidance and this was in keeping with the patient population in Whelton *et al*. Pfizer, therefore appealed against the Panel's ruling of a breach of Clause 8.1.

Pfizer noted the Panel's review of its use of the Whelton *et al* (2004) data on page three of the leavepiece. Pfizer agreed that both Celebrex and rofecoxib were compared with placebo but it could not agree with the Panel's suggestion that it gave the impression that Celebrex and rofecoxib had been directly compared. Pfizer submitted that it had not made such a comparison and it had deliberately used colour coding to distinguish between them. Moreover, the confidence intervals clearly did not overlap. [At the appeal Pfizer acknowledged that the confidence intervals did overlap]. The heading 'Differences in the risk of CV events' referred to the fact that Celebrex was not found to be different from NSAIDs in terms of risk of acute MI or stroke in hypertensive patients, whereas rofecoxib was.

Based on the above, Pfizer submitted that its use of the Whelton data was not an unfair representation, was not misleading with respect to the reported effect of Celebrex or rofecoxib and in no way disparaged rofecoxib.

Pfizer submitted that the data were clearly referenced and valid. Pfizer contested Merck Sharp & Dohme's assertion and the Panel's agreement that the use of such a database of over three million patients was not

valid and could not be used because it was a retrospective analysis. It was on the basis of data derived in this way that prescribing and formulary decisions were made every day, and studies such as these in vast numbers of patients informed prescribers about safety. Indeed, very rare adverse events were often detected by studies such as these, which added to the safety database of a particular medicine.

Pfizer submitted that rofecoxib's significantly worse outcome compared to both conventional NSAIDs and non-NSAID therapy as shown in the Whelton data had been borne out by the recent precipitate withdrawal of rofecoxib at all doses and for all indications from the global market place.

Pfizer therefore appealed the Panel's ruling of breaches of Clauses 7.2 and 8.1.

With regard to the Panel's rulings on the statement 'Differences in the risk of MI', the commonest doses of Celebrex and rofecoxib used in Solomon *et al* were ≤200mg and ≤25mg respectively. This was a study performed on patients taking these medicines as they were used in real life. It was an undeniable fact that such medications were used at doses above those recommended and Vioxx 50mg was a dose that was actually used in OA/RA patients (DIN-LINK, MAT June 2004). The study reported on the risk of a hard endpoint, namely MI.

Pfizer could not understand the Panel's comments with regard to patients over the age of 65 being included in this study. It was this very age group who were most likely to receive Celebrex or rofecoxib, because this was the age group with OA and because the NICE guidance specifically recommend their use in this age group. Pfizer submitted that it had presented an accurate view of the findings of the study and that the inclusion of this study in the leavepiece was acceptable. Pfizer, therefore, appealed the Panel's ruling of breaches of Clauses 7.2 and 8.1.

Pfizer noted the Panel's review of Pfizer's use of White *et al* (2003). The Panel had repeated the potential limitation of the study quoted by Merck Sharp & Dohme and commented that it was concerned that the reader could gain the impression that the CV safety profile of Celebrex was comparable to placebo and that given the cautions given by the authors, the bar chart was not a fair reflection of White *et al*. Pfizer submitted that Merck Sharp & Dohme had quoted the authors' reservations selectively and that the Panel had repeated this mistake.

Pfizer noted that, as the Panel had pointed out, however, that the authors went on to state that the potential deficit was compensated, at least in part, by the availability and use of original source data for CV events. The authors concluded that the data showed no evidence for a difference in the incidence of CV events between Celebrex and NSAIDs or Celebrex and placebo.

Pfizer submitted that its presentation of the data accurately presented the study results and it had not made any claims based on this graph other than 'even at supra-therapeutic doses, Celebrex has no significant difference to NSAIDs in the incidence of serious CV thrombo-embolic events'.

Pfizer did not accept that the heading 'Celebrex: cardiovascular safety' implied the 'safety' of Celebrex with regard to the cardiovascular system. It was quite clearly a heading informing the reader that the page would discuss safety issues with regard to Celebrex. This was evidently in keeping with the page and with the whole leavepiece. It did not state that Celebrex was safe.

Pfizer noted the Panel's comment that 'the reader would gain the impression that the CV safety profile of Celebrex was comparable to placebo and that was not so'. Pfizer did not consider that the reader would make such an extrapolation and it, therefore, appealed the Panel's ruling of a breach of Clause 7.2.

Pfizer noted that in the Panel's review of its use of the Ray *et al* data on page 5 of the leavepiece the Panel had correctly noted that three of the points referred to high dose rofecoxib (>25mg) and had queried the use of these data. Pfizer agreed that the maximum recommended dose of rofecoxib in OA/RA was 25mg but market data (DIN-LINK, MAT June 2004) showed that a significant percentage of Vioxx 50mg (12% of the use of Vioxx 50mg for all diagnoses) was used in OA and RA patients. Moreover, as clearly outlined in the text of the leavepiece, rofecoxib was licensed for acute pain at the dose of 50mg. Pfizer disagreed with the Panel that the quotation of rofecoxib data at the higher dose in any way disparaged rofecoxib and so appealed the Panel's ruling of a breach of Clause 8.1 in this regard.

Pfizer submitted that it was not its intention with this leavepiece to give 'the impression that there was no need to worry about the cardiovascular tolerability profile of Celebrex', what it had attempted to communicate was that the CV profile of Celebrex was no worse than that seen with NSAIDs and that rofecoxib's cardiovascular profile had largely been shown to be worse than NSAIDs and Celebrex. Subsequent events had vindicated this point of view.

Pfizer submitted that it had ensured that every page was printed with a warning regarding the prescription of NSAIDs and COX-2s in patients with CV disease and that Celebrex was contra-indicated in severe CHF, as was reflected in the SPC and in the prescribing information printed on the back page of the leavepiece.

Pfizer submitted that its customers had consistently received misleading information from competitor companies about the CV safety profile of Celebrex, particularly in comparison to rofecoxib and it was obliged to counter such attacks on its product whose benefit-risk profile it considered continued to be favourable.

COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme asserted that Pfizer remained in breach of the Code. Pfizer had claimed that the voluntary worldwide withdrawal of Vioxx vindicated its position. This withdrawal was based solely on the safety data from a placebo controlled study (APPROVe) with Vioxx 25mg in which the increase in adverse outcomes was not evident until after 18 months of continuous treatment. On preliminary

analysis, this increase in thrombotic cardiovascular events did not correlate to patients with hypertension, although Pfizer based much of its argument on apparent blood pressure differences between rofecoxib and celecoxib.

Merck Sharp & Dohme alleged that Pfizer made some extremely confident statements regarding CV risk based on retrospective observational studies and randomised controlled trials of limited duration. Pfizer noted that there were no controlled clinical trial data with celecoxib extending to eighteen months continuous treatment and it was surprising that Pfizer continued to base its advertising on claims of CV safety using short term clinical trials and epidemiological studies as the 'evidence base'. The bias and limitations inherent in observational studies were well known. As the cause of the increased CV risk after 18 months of continuous therapy with rofecoxib 25mg verses placebo in patients with a history of colorectal adenoma was undetermined and the pharmaceutical industry was subject to intense scrutiny, it was essential that it acted responsibly rather than risk bringing the industry into disrepute.

The statement 'Differences in blood pressure' on page two was linked to Whelton *et al* 2001 in which elderly hypertensive patients ≥ 65 years of age were treated for 6 weeks with either celecoxib 200 mg once daily or rofecoxib 25 mg once daily. Blood pressure measurements were taken 24 hours after dosing at 1, 2 and 6 weeks. Merck Sharp & Dohme agreed with the Panel that the doses of the two medicines were not comparable. The starting dose in OA for celecoxib was 200 mg per day, rising to 400 mg per day if necessary. The doses for rofecoxib were 12.5 mg daily to start, rising to 25 mg daily if necessary. In the study, the starting dose of celecoxib was compared with the top dose of rofecoxib which was administered without titration. The Vioxx dose was contrary to the product licence and the SPC. Both Celebrex and Vioxx SPCs recommended that the lowest effective dose should be used in hypertensive patients. Whelton *et al* introduced rofecoxib at the higher recommended dose, contrary to the SPC precaution.

Merck Sharp & Dohme stated that provision of market data did not alter the inequalities and the limited details of prescriptions for one month were irrelevant. Information that, excluding VioxxAcute, approximately 50% of prescriptions were for Vioxx 12.5mg and 50% were for 25mg had not assisted any argument. Knowing the split between Celebrex 100mg and 200mg capsules was of no value in determining total daily dose as the medicine could be taken once or twice daily in a range from 100mg to 400mg per day. The SPC provided the definitive information regarding a product and advertising should be based upon the SPC.

Whelton *et al* (2001) measured blood pressure 24 hours after dosing, yet this time point was two to three half-lives after the celecoxib dose, when any effect of blood pressure could be expected to have disappeared (the half-life for celecoxib was 8-12 hours). Conversely, blood pressure was measured 1.4 half-lives after the administration of rofecoxib (half-life 17 hours), when any effect on blood pressure would be closer to its peak.

Merck Sharp & Dohme noted that approximately 10% more antihypertensive medications were taken by celecoxib patients than by rofecoxib patients during the study (celecoxib: 668 medications in 412 patients; rofecoxib: 606 medications in 399 patients). It was not clear from the paper how robustly these differences were tested for statistical significance. However, the number of patients taking ACE inhibitors was significantly greater in the celecoxib group (celecoxib 40.3%. rofecoxib 29.1%, $p<0.05$). It was highly possible that the differences in concomitant antihypertensive medication could have affected two of the study primary endpoints, namely predefined changes in systolic and diastolic blood pressure, by altering the stability of blood pressure control.

Merck Sharp & Dohme noted that in Whelton *et al* (2001) there were three primary endpoints: significant oedema ($p = 0.014$); elevated systolic blood pressure ($p = 0.032$); elevated diastolic blood pressure ($p = 0.44$).

The statistical protocol for correction for multiple analyses was not stated in the paper, but it was well accepted as a convention of basic statistical principles that where more than one primary endpoint was employed, the combined p value should not exceed 0.05 and that the correction protocol should be pre-defined. It was possible that oedema ($p=0.014$) did meet the pre-defined significance value, but highly unlikely that the elevation of systolic blood pressure was statistically significant after allowing for multiple endpoints. The elevation of diastolic blood pressure was not statistically significant by any standards. Thus, at best, it was likely that only the development of oedema reached statistical significance, and the other two primary endpoints did not. To further complicate matters, three endpoints were mentioned in the abstract but in the statistical analyses section of the methodology only two endpoints were described, namely oedema and hypertension. Hypertension was then separately analysed as its systolic and diastolic components, presumably to achieve statistical significance.

Merck Sharp & Dohme strongly supported the Panel's finding that Whelton *et al* (2001) represented an unfair comparison of Celebrex and Vioxx, disparaged Vioxx and was in breach of Clause 8.1 of the Code.

Page three of the leavepiece beneath the heading 'Differences in the risk of CV events', the data from Whelton *et al* in 2004 based on figures from January 1999 to June 2001. This retrospective analysis was performed on an American claims database, a point that should have been highlighted as the findings might not apply to the British population. Merck Sharp & Dohme stated that it was impossible to exclude bias and confounding from such an analysis.

As noted by the Panel, it was not stated whether the difference between celecoxib and rofecoxib was statistically significant; the confidence intervals for rofecoxib (1.71-3.51) and celecoxib (0.98-1.86) clearly overlapped, despite Pfizer's claim that they had not. In the context of the entire promotional item, the impression given was that the CV safety of celecoxib and rofecoxib had been directly compared and found to be statistically significantly different, a distinction

reinforced, as the Panel stated, by the heading 'Differences in the risk of CV events'.

Although the database included 3 million patients, the number of individuals on each medication was surprisingly low (841 on rofecoxib and 1288 on Celebrex). Such numbers were well within the remit of those recruited for a randomised controlled trial and thus one of the purported benefits of using a retrospective analysis (the inclusion of a cohort of patients far larger than could be followed in a randomised controlled trial) was lost.

Merck Sharp & Dohme alleged that importantly, there was no mention of dose in the abstract which was a strange and crucial omission, bearing in mind the Vioxx SPC statement that 'fluid retention, oedema and hypertension…appear to be dose related'. Merck Sharp & Dohme therefore agreed with the Panel's finding that this section was misleading and disparaging in breach of Clauses 7.2 and 8.1 of the Code.

Merck Sharp & Dohme noted on page three of the leavepiece under the heading 'Differences in the risk of MI', the problem with Solomon *et al* (2004) was not that the patients were over 65 years of age. It was the fact that, as stated by the Panel that excessively high doses were used in these individuals in comparison to the SPC recommendations. The Vioxx SPC stated that 'a daily dose of 25mg should not be exceeded' in osteoarthritis, and that 'care should be exercised when increasing the daily dose from 12.5mg to 25mg in the elderly'. This was in distinction to the Celebrex SPC where the 400mg dose was listed for both OA and RA and in the elderly 'the dose might, if needed, later be increased to 400mg per day'. Pfizer argued that doses of rofecoxib >25mg were used in this 'real life situation', therefore the results were valid. Merck Sharp & Dohme alleged that as these data used an unlicensed dosage of rofecoxib, such data should not be used in promotional material. In any event, the data used in the analysis were from the USA and Pfizer's own prescription data from the UK indicated that only a tiny minority of UK patients (35 out of 7332 OA patients) were prescribed this high (unlicensed) dose. Furthermore, while the age of the patients *per se* was not a reason to disagree with the use of this study, the dosing regimens employed in these 'at risk patients' were not applicable to the UK SPC or UK clinical practice.

Merck Sharp & Dohme alleged that this was a retrospective examination of an American database, not a 'study performed on patients' as claimed by Pfizer in its appeal. Confounding could not be eliminated. The authors stated that 'several variables of interest were not available within the study database, including body mass index, tobacco use, aspirin use and socioeconomic status. In theory these variables could be differentially related to the use of a coxib, use of an NSAID and AMI' [acute myocardial infarcation]. They were unequivocally related, at least to risk of MI, and were inadequately controlled for by looking at a separate 'in home survey' from 1999.

Merck Sharp & Dohme alleged that an elevated risk of MI with rofecoxib within the first 30 days of use was different from the findings of other trials. The scientific rational for this 30 day finding from a study which could only be hypothesis generating, not testing, was unclear. This selection of data was not representative of the totality of evidence even within the remit of observational studies (eg Mamdani *et al* 2003, quoted by Solomon, showed no increased risk of AMI with rofecoxib). The pooled analysis of randomised controlled trials by Weir *et al* 2003 demonstrated that rofecoxib was not associated with an excess of CV thrombotic events compared with either placebo or non-naproxen NSAIDs. This was further supported by the recent analysis of the APPROVe study which showed no difference in CV adverse events from placebo over the first 18 months.

Therefore, Merck Sharp & Dohme agreed with the Panel that, through making unbalanced comparisons that disparaged rofecoxib, Pfizer was in breach of Clauses 7.2 and 8.1.

Merck Sharp & Dohme agreed with the Panel that the heading on page five of the leavepiece 'Celebrex: cardiovascular safety' was potentially misleading in breach of Clause 7.2. It reinforced the overall impression from the detail aid that Celebrex was 'safe' with regard to the CV system.

Merck Sharp & Dohme alleged that the graph adapted from White *et al* (2003) was confusing and gave prescribers the impression that the CV safety of Celebrex was comparable to placebo. The majority of the Celebrex trials, as detailed in White *et al* paper, were of up to 12 weeks in duration. There were two trials which lasted 24 and 26 weeks, in stark contrast to the three year trial with Vioxx. The statement 'even at supratherapeutic doses, CELEBREX has shown no significant difference to NSAIDs' needed to be qualified with a detailed description of these doses and the proportion of patients involved.

Merck Sharp & Dohme supported the Panel's view that the portrayal was misleading in breach of Clause 7.2.

Merck Sharp & Dohme noted that the retrospective study Ray *et al* (2002) was placed on page six below a heading describing 'emerging data'. The Panel had noted that the first three bullet points 'clarifying the relative risks of CHD' related only to supratherapeutic doses of rofecoxib that were outside the terms of the SPC. Contrary to Pfizer's appeal, in the UK in June 2004 (using the numbers supplied by Pfizer with its appeal) only 47 of a total of 9134 prescriptions for OA and RA combined were written for rofecoxib >25mg. The 50mg dose of rofecoxib was licensed only for acute pain and there was no evidence that acute use (which by definition was short term) of rofecoxib was associated with CHD. The dose dependent nature of adverse events was well documented and this page therefore disparaged rofecoxib.

Merck Sharp & Dohme alleged that the fourth bullet point was inaccurate, describing a dose of ≤ 25mg as 'low dose rofecoxib'. This was the highest dose of rofecoxib licensed for chronic use in OA and RA. Rephrasing this bullet point appropriately would read: 'There was no increased risk of serious CHD for users of celecoxib or rofecoxib at licensed doses (≤ 25mg daily) compared with non-NSAID users' which would be a fair reflection of all available data at the time the detail aid was produced.

Merck Sharp & Dohme alleged that the statement breached Clause 7.2 and 8.1, as ruled by the Panel.

Merck Sharp & Dohme alleged that Pfizer's concluding remarks in its appeal demonstrated its intention to unfairly disparage rofecoxib and highlighted its breach of Clause 8.1. 'What Pfizer attempted to communicate was that the cardiovascular profile of Celebrex was no worse than that seen with NSAIDs and that rofecoxib's cardiovascular profile had largely been shown to be worse than NSAIDs and Celebrex'. Rofecoxib had not been demonstrated to be statistically worse in terms of cardiovascular profile than other NSAIDs. Merck Sharp & Dohme alleged that Pfizer's statement could not be justified by the results of a 3 year randomised controlled trial of rofecoxib versus placebo that was not available until after it had produced the leavepiece in question.

Merck Sharp & Dohme noted Pfizer's argument, there were 'very important differences' between the SPCs for Celebrex and Vioxx, with hypertension listed as an uncommon undesirable effect for celecoxib and common for rofecoxib. However, this information was obviously available to the CPMP, when, following a detailed review, it harmonised the wording of the SPCs for the coxib class, so that Section 4.4 read: 'Caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction and hypertension'.

APPEAL BOARD RULING

In relation to the section headed 'Differences in blood pressure' on page 2 and the claim beneath 'Celebrex produced a significantly lower mean systolic blood pressure change compared with rofecoxib in elderly hypertensive patients with OA', the Appeal Board noted that in Whelton *et al* (2001) the dose of rofecoxib used, at 25mg per day, was the maximum recommended dose for OA. The Vioxx SPC stated that the recommended adult starting dose was 12.5 mg once daily. The SPC also stated that in elderly patients (> 65 years old) the lower dose (12.5mg per day) should be used initially and that care should be exercised when increasing the daily dose from 12.5mg to 25mg in the elderly. Conversely the dose of Celebrex (200mg once daily) was the lowest recommended dose. The Appeal Board noted Pfizer's submission about the significant usage of 25mg Vioxx in the OA and RA population. Nonetheless, given the products' respective SPCs the Appeal Board considered that the doses used in Whelton *et al* (2001) represented an unfair comparison of Celebrex and Vioxx and in that regard page two of the leavepiece disparaged Vioxx. The Appeal Board upheld the Panel's ruling of a breach of Clause 8.1. The appeal on this point was unsuccessful.

The Appeal Board noted page three of the leavepiece which was headed 'Differences in the risk of CV events' below which was a graph adapted from Whelton *et al* (2004) which showed the relative risk of acute MI or stroke in 5,521 patients with OA or RA being treated for hypertension; the relative risks were rofecoxib 2.45, Celebrex 1.35, NSAID 1.11 and a non-NSAID 1.0. The relative risk of rofecoxib was illustrated by a red line; a box in red to the right of the graph read 'Significant increase in the risk of acute MI or stroke with rofecoxib compared with non-users in treated hypertensive patients with OA or RA'. The relative risk of celecoxib similarly illustrated by a shorter green line; a green box to the left of the graph read 'No significant difference in the risk of acute MI or stroke in users of CELEBREX compared to non-users in treated hypertensive patients with OA or RA'.

The Appeal Board considered that the impression was that the CV safety of rofecoxib and Celebrex had been directly compared and found to be statistically significantly different. No such comparison had been made. The impression of a proven clinically statistically significant difference was reinforced by the heading 'Differences in the risk of CV events'. In addition the green and red colour scheme implied a comparison between the two products.

The Appeal Board considered that the graph on page three of the leavepiece represented a misleading and unfair comparison of rofecoxib and Celebrex and in that regard disparaged rofecoxib. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 8.1. The appeal on this point was unsuccessful.

The Appeal Board noted the subheading 'Differences in the risk of MI' on page three above a section which discussed Solomon *et al* (2004). Solomon *et al* included patients aged 65 years and over some of whom had taken rofecoxib at doses of greater than 25mg. The Appeal Board noted its comments above with regard to the recommended dose of rofecoxib in the elderly. The Appeal Board further noted that an elevated risk of MI with rofecoxib within the first 30 days of use did not reflect the findings of Mamdani *et al* (2003) or Weir *et al* (2003). The data presented did not reflect the balance of the evidence.

The Appeal Board thus considered that, given the age of the patients and the doses of rofecoxib used, the results of Solomon *et al* did not represent a fair and balanced comparison of rofecoxib and Celebrex that regard disparaged rofecoxib as alleged. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 8.1. The appeal on this point was unsuccessful.

The Appeal Board noted the heading 'Celebrex; cardiovascular safety' on page four beneath which a bar chart compared the cardiovascular thrombotic adverse events endpoints for all patients whether or not they were taking aspirin. The results shown were Celebrex vs placebo (p=ns) and Celebrex vs NSAIDS (p=ns). The bar chart was adapted from White *et al* (2003) which was described as an analysis of 15 controlled arthritis clinical trials for Celebrex (n=31,879). The Appeal Board noted that White *et al* (2003) highlighted potential limitations of this meta analysis.

The Appeal Board was extremely concerned that the bar chart gave the impression that there was no statistically significant difference between Celebrex and placebo and NSAIDs in relation to CV thrombotic adverse events. The reader would gain the impression that the CV safety profile of Celebrex was comparable to placebo and that was not so. The Appeal Board considered that this impression was

compounded by the claim beneath the bar chart 'Even at supratherapeutic doses, CELEBREX has shown no significant difference to NSAIDs in the incidence of serious CV thromboembolic events'. Given the caution expressed by White *et al*, the bar chart was not a fair reflection of the study and the overall impression was inconsistent with the CV safety profile of Celebrex as set out in its SPC that 'As with other COX-2 inhibitors and traditional NSAIDs caution should be exercised in patients with cardiovascular disease. Celebrex is contraindicated in severe congestive heart failure'. The Appeal Board considered that the heading 'Celebrex: cardiovascular safety' compounded the overall impression given and was misleading in this 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 three of the four bullet points on page five of the leavepiece related to high dose rofecoxib use which was defined as >25mg, acute pain dosage. The Appeal Board noted the Vioxx SPC stated that a daily dose of 25mg should not be exceeded in OA; for RA the maximum recommended dose was 25 mg and in the elderly care should be exercised when increasing the daily dose from 12.5mg to 25mg. The relevance of the high dose data to the UK population was queried.

The Appeal Board was also very concerned about the second bullet point 'The risk of serious CHD increased by 70% relative to non-users in the high dose rofecoxib group (p=NS)'; the difference was non-significant and although this had been clearly stated, a 70% increase in risk was of such magnitude that a reader might nonetheless attach weight to it despite the fact that it was possibly a chance finding.

The Appeal Board considered that page 5 represented an unfair criticism of rofecoxib and was thus disparaging as alleged. The Appeal Board upheld the Panel's ruling of a breach of Clause 8.1. The appeal on this point was unsuccessful.

REPORT FROM THE PANEL TO THE APPEAL BOARD

The Appeal Board was extremely concerned that the leavepiece gave the impression that there was no need to worry about the cardiovascular tolerability profile of Celebrex. This was not so. The Celebrex SPC advised caution in patients with a history of ischaemic heart disease, cardiac failure, left ventricular dysfunction or hypertension. The product was contraindicated in severe CHF. The barchart on page 4 of the leavepiece implied that there was no statistically significant difference between the cardiovascular safety of Celebrex and placebo. In the Appeal Board's view the leavepiece was such that patient safety in relation to the use of Celebrex could be compromised. This was a serious matter.

The Appeal Board noted that the leavepiece would have been left with a number of GPs, and other health professionals. The Appeal Board was very concerned that health professionals would be left with a misleading impression of the safety profile of Celebrex that was inconsistent with its SPC. The Appeal Board decided to require Pfizer to take steps to recover the leavepiece as set out in Paragraph 10.3 of the Constitution and Procedure. The Appeal Board decided that Pfizer should write to each health professional to whom the leavepiece had been detailed, and therefore, potentially left with, to give details of the case and to request, where practicable, return of the leavepiece. The Appeal Board decided that Pfizer should supply the draft letter to the Authority so that the wording could be agreed before its distribution. The letter should be sent as soon as possible.

Further, the Appeal Board decided that the matter should be reported to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure. The Appeal Board considered that it would have required Pfizer to issue a corrective statement if it had the power to do so. The Appeal Board therefore recommended that the ABPI Board consider such an option.

REPORT FROM THE APPEAL BOARD TO THE ABPI BOARD

The ABPI Board noted that the Appeal Board had required Pfizer to recover the leavepiece. The letter sent on 7 February had been agreed with the Authority. The ABPI Board was concerned that the letter did not give the impression that Pfizer agreed with the rulings. The ABPI Board noted Pfizer's submission that the EMEA and FDA were reviewing Celebrex data with a report expected later in February. The ABPI Board considered that taking all the circumstances into account the publication of a corrective statement could cause confusion amongst health professionals.

The ABPI Board considered that Pfizer should have acted more promptly in relation to the issue of the letter and formal changes to its systems. The company representative regretted that the leavepiece had not been withdrawn earlier. The ABPI Board was very concerned about this matter which involved patient safety and decided that Pfizer should be publicly reprimanded.

Complaint received	**26 July 2004**
PMCPA Proceedings completed	**4 January 2005**
ABPI Board Proceedings completed	**9 February 2005**

CASE AUTH/1617/8/04

GENERAL PRACTITIONER/DIRECTOR v WYETH

Alleged breach of undertaking and conduct of representatives

A general practitioner alleged that a switch programme offered by two representatives from Wyeth was in breach of an undertaking previously given by that company in Case AUTH/1561/3/04. Case AUTH/1561/3/04 concerned a switch programme whereby patients on Zoton capsules (lansoprazole) were switched to Zoton FasTab. As this aspect of the complaint concerned a breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings.

The complainant also alleged that whilst the representatives made the short-term benefits of switching patients to Zoton FasTab clear, the long-term financial penalty was misrepresented. The representatives calculated that a generic alternative to Zoton would not be available for approximately 5-6 years. The complainant considered that the financial advantage for Zoton FasTab would be lost as soon as a generic version became available.

Wyeth submitted that the service to which this complaint related was part of a new service which the company had developed further to the outcome of Case AUTH/1561/3/04.

The Panel noted that the complainant had, *inter alia*, alleged a breach of the undertaking given by Wyeth in Case AUTH/1561/3/04 which concerned a switch programme whereby patients on Zoton capsules were switched to Zoton FasTab; breaches of the Code had been ruled. The Panel considered that its ruling in a previous case, Case AUTH/1606/7/04, was relevant; Case AUTH/1606/7/04 concerned whether arrangements for Wyeth's revised switch programme were in breach of the undertaking given in Case AUTH/1561/3/04.

In Case AUTH/1606/7/04 the Panel had noted that there were differences between the switch programme at issue in Case AUTH/1561/3/04 and that at issue in Case AUTH/1606/7/04; the revised service was not restricted to a switch from Zoton capsules to Zoton FasTab but was available for any oral proton pump inhibitor (PPI) of the doctor's choice. The Panel noted Wyeth's submission that the prescribing decision of the GP had to be made in writing in advance of the offer of the service. The medication review booklet explained that the Gastrocare service was available to review any oral PPI dose at the request of the practice. The representatives' 'Action plan: Gastrocare service offerings' explained that if the GP chose to change from one formulation of a PPI medication to another in a dose for dose switch, the most suitable service was the GP System Specialist Implementation. If any other change was required, or if the GP did not wish for this service, the GP was offered the Gastrocare Audit Review.

The Panel had considered that the service at issue in Case AUTH/1606/7/04 was sufficiently different from that considered in Case AUTH/1561/3/04; the service was no longer restricted to switches from Zoton capsules to Zoton FasTab but was available for all oral PPIs. The Panel had considered that there was no breach of the undertaking previously given and no breaches of the Code had been ruled.

Turning to the present case, Case AUTH/1617/8/04, the Panel noted Wyeth's submission that the material and service offering at issue in the present case were the same as those considered in Case AUTH/1606/7/04. The Panel thus considered that its ruling in Case AUTH/1606/7/04 applied here. No breaches of the Code were ruled.

In relation to the allegation that the long-term financial penalty of switching patients was misrepresented, the Panel noted Wyeth's submission that the position was very complicated and could not be identified with certainty. The Panel also noted Wyeth's submission that the representatives were careful to include appropriate caveats reflective of the speculative nature of the discussion.

The Panel considered that, irrespective of any caveats applied by the representatives, supposition was not a reasonable basis upon which to make promotional claims and had the potential to mislead. The Panel considered the discussion about the long-term financial consequences of switching was misleading; a breach of the Code was ruled. The representatives had not maintained a high standard; a further breach was ruled.

A general practitioner complained about the activities of two representatives from Wyeth Pharmaceuticals in relation to a Zoton (lansoprazole) switch programme.

The complainant referred to an article in the BMJ, 26 June 2004 which reported that the Authority had found that Wyeth had breached the Code in asking general practitioners to sign a consent form allowing a third party to use the practice computer system to switch patients from Zoton capsules to Zoton FasTabs [Case AUTH/1561/3/04].

As the complaint involved an alleged breach of undertaking that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Code of Practice Appeal Board.

COMPLAINT

The complainant stated that at a meeting in his practice in July, exactly the same offer was made by two Wyeth representatives. The representatives repeatedly pressed their case for switching patients in spite of the doctors' obvious reluctance and indication that they would discuss the matter with their pharmaceutical advisor. The short-term financial benefits of switching patients in this manner were made clear, but the long-term financial penalty was, in the complainant's view, misrepresented.

When writing to Wyeth, the Authority asked it to respond in relation to Clauses 2, 7.2, 15.2 and 22 of the Code.

RESPONSE

Wyeth confirmed that it had fully complied with the undertaking it gave in respect of Case AUTH/1561/3/04. The Formulary Based Implementation (FBI) service and all associated materials in respect of which the undertaking was given were withdrawn with immediate effect from the sales force by memorandum and the FBI service had not been offered nor materials used since June 2004. Wyeth provided the relevant documentation. Wyeth's regional business managers were also given a presentation at their quarterly management meeting on the outcome of Case AUTH/1561/3/04 and the new service offering in order that they were fully aware of the changes to be made.

The service to which this complaint related was part of the new service which Wyeth subsequently designed and developed in order to avoid further breaches of the Code following the outcome of Case AUTH/1561/3/04. This was the same service as the one that was the subject of a complaint being dealt with in Case AUTH/1606/7/04 as an alleged breach of undertaking.

In Wyeth's opinion, the revised service and associated material were fully Code compliant and it confirmed that the service carried out by the Wyeth representatives during the meeting with the complainant was fully in accordance with Code compliant company procedures and material.

Following the provision of the undertaking in Case AUTH/1561/3/04, Wyeth's service range relating to the gastro-intestinal therapy area had been redesigned and developed, and the new range launched, so that all such services offered were non-brand specific and therefore could be offered and performed in respect of any relevant 'brand' of medicine (ie proprietary or generic) of the GP's choice. Further, the new material and the material use sequence now made it clear that the prescribing decision of the GP had been made in writing in advance of any offer of a service to assist in implementing that decision being made by Wyeth. The Wyeth service now clearly fell under the provisions of the supplementary information to Clause 18.1 of the Code and was, in Wyeth's opinion, compliant with the provisions of that clause which allowed the provision of medical and educational services which would enhance patient care or benefit the NHS if they were provided in such a way as to not be an inducement to prescribe any medicine.

The designated procedure for the new service was as follows:

The GP expressed an interest in a review of their or their practice's proton pump inhibitor (PPI) prescribing. In a visit separate to any product-related visit, or in a clearly separated part of the same visit, and following confirmation from the GP that they had an interest in a review of their or their practice's PPI prescribing, the representative followed the procedure as set out in the representatives' briefing document 'Action Plan: GastroCare Service Offerings' (ZZOT3580) and the GastroCare Process Flowchart (ZZOT3601), the relevant pages of which were provided.

Briefly, the GP completed and signed the Medication Review Spreadsheet (ZZOT3587) to illustrate the prescribing decision s/he had made or was making and wanted to implement. If the only change the GP wished to make, as shown by the completed Medication Review Spreadsheet, was that of changing prescribing from one formulation of the same PPI to another in a dose for dose switch, then to assist the GP in implementing that prescribing decision the representative offered the service most appropriate to that type of change, in this case the GP Systems Specialist Implementation (GPSSI) service, using the GPSSI Pack (ZZOT3588) to show the GP how the service would be carried out. If the GP decided to accept the service offering, the Practice Booking and Consent Form was completed by the GP and arrangements then made by the Wyeth representative with an external supplier to carry out the service at the practice.

In respect of the meeting referred to by the complainant, the practice did not request that such a service be provided and so a Booking and Consent Form for the GPSSI service was not completed.

Wyeth stated with regard to the first allegation, that the representatives 'repeatedly pressed their case …in spite of the doctors' obvious reluctance', referred to the product-related part of the meeting rather than to any discussions relating to the offering of any service provision. The representatives had confirmed that during this part of the meeting they discussed the relative costs of Zoton FasTab and Zoton capsules as set out in the cost leavepiece (ZZOT3543) and therefore the benefits of the practice switching from the prescribing of Zoton capsules to Zoton FasTab. The representatives had confirmed that in their opinion the practice willingly accepted and agreed with the inherent cost benefits of Zoton FasTab as discussed and therefore the resultant cost saving that could be incurred by switching from Zoton capsules to Zoton FasTab. As stated in Case AUTH/1561/3/04, the Panel had agreed that a company could promote products on the basis of cost and that it was not unreasonable to note savings that a practice might make by switching from one product to another.

The representatives believed that their promotional activity was entirely in the normal course of business and that no pressure was applied to the practice as alleged. The representatives had also confirmed that the practice informed them at the meeting that any further action needed to be discussed with the pharmaceutical advisor and that the practice would contact one of the representatives following such discussions. The representatives accepted this decision and left the meeting believing that it had been a positive one.

Wyeth stated that it could not make specific comments about the allegation that the long-term financial penalty was misrepresented as no details of this aspect of the complaint were given. However, the representatives had confirmed that the leavepiece used for the cost-benefit discussion was that referred to above (ZZOT3543) which clearly and accurately set out the relative cost savings of prescribing Zoton FasTab. Any short- or long-term cost benefits could

be ascertained independently by the recipient(s) of any such information in accordance with their own short-term prescribing policy and long-term strategy.

Based on the above, it was Wyeth's opinion that there had been no activity or materials associated with promotion which had brought discredit upon, or reduced confidence in, the pharmaceutical industry and therefore no breach of Clause 2 of the Code. High standards were maintained at all times both by the conduct of the representatives and by the content and use of all material associated with product promotion and the relevant service offering which contained only information and claims which were accurate, fair, balanced, objective and unambiguous and therefore there had been no breach of Clauses 7.2 or 15.2. Wyeth had ensured that it had complied with all aspects of the undertaking given in respect of Case AUTH/1561/3/04 and hence there had been no breach of Clause 22 of the Code.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant was asked for further details in relation to the allegation that the long-term financial benefit was misrepresented. The complainant explained that it was generally accepted that lansoprazole would come off licence in the near future (within the next year). The complainant stated that the representative did some calculations which indicated that a generic alternative would not be available for approximately five to six years. Clearly, the financial advantage of Zoton FasTab would be lost as soon as a generic version became available. This was the misrepresentation of the long-term financial penalty.

FURTHER COMMENTS FROM WYETH

Wyeth explained that the representatives in question confirmed that during the discussion of the relative costs of Zoton FasTab and Zoton capsules the lansoprazole patent position was raised. The representatives advised that they responded to this accurately by confirming that the first patent relating to lansoprazole was due to expire in a year.

The discussion then moved on to when a generic alternative would be available that would provide cost savings for the practice. Here various factors were discussed including the time before the first generic might enter the market (there was of course more than one lansoprazole patent and so exactly when a generic would be able to enter the market was uncertain) and then the time it could take before the tariff price for generic lansoprazole capsules was reduced to a level where the practices enjoyed significant cost savings in comparison to Zoton FasTab, which could possibly be up to 3 to 5 years away. The representatives were careful to include appropriate caveats reflective of the speculative nature of the discussion.

The representatives did not indicate that a generic alternative would not be available for approximately 5 to 6 years and Wyeth did not accept that the representatives misrepresented the position on generic availability.

As with any discussion on generics and generic savings, the position was complicated and could not be identified with certainty. As would appear to be the case here, misunderstandings could easily arise and this was why the company did not speculate on this in its material and had briefed its representatives to try to avoid being drawn into speculation on the matter also.

PANEL RULING

The Panel noted that the complainant had, *inter alia*, alleged a breach of the undertaking given by Wyeth in Case AUTH/1561/3/04. Case AUTH/1561/3/04 concerned a switch programme whereby patients on Zoton capsules were switched to Zoton FasTab; breaches of Clauses 9.1 and 18.1 of the Code were ruled.

The Panel considered that its ruling in a previous case, referred to by Wyeth, Case AUTH/1606/7/04 was relevant; Case AUTH/1606/7/04 concerned whether arrangements for Wyeth's revised switch programme were in breach of the undertaking given in Case AUTH/1561/3/04.

Panel ruling in Case AUTH/1606/7/04

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 the industry that companies complied with undertakings.

The Panel noted that the previous case, Case AUTH/1561/3/04, concerned the FBI service whereby patients on Zoton capsules were switched to Zoton FasTab. The Panel had considered that the FBI Service was part of the promotion of Zoton FasTab; it was not described as anything else in the material. The service could thus not benefit from the supplementary information to Clause 18.1 regarding the provision of medical and educational goods and services. The Panel noted Wyeth's submission that Zoton FasTab was 10% less expensive than Zoton capsules. Switching patients from Zoton capsules to Zoton FasTab was thus a less expensive way of prescribing Zoton. Companies could of course promote products on the basis of cost and it was not unreasonable to note savings that a practice might make by switching from one product to another. The difficulty was when the company paid directly or indirectly for those changes to be made because then the company's actions amounted to it paying to boost the prescription of a specific medicine. In this regard, the Panel noted that the switch programme at issue involved two products marketed by the same company; prescriptions for Zoton FasTab were not being generated at the expense of another company's product. Nonetheless, Clause 18.1 of the Code stated that 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend or buy any medicine, subject to the provisions of Clause 18.2'. Thus in the Panel's view it was immaterial that the two medicines at issue were marketed by the same company. The provision of the

FBI Service by Wyeth would benefit a practice by saving it the expense of carrying out the switch itself. The arrangements amounted to a pecuniary advantage given as an inducement to prescribe Zoton FasTab. Breaches of Clauses 9.1 and 18.1 had been ruled.

The Panel noted that there were differences between the switch programme at issue in Case AUTH/1561/3/04 and the service at issue in the present case, Case AUTH/1606/7/04; the present service was not restricted to a switch from Zoton capsules to Zoton FasTab but was available for any oral PPI of the doctor's choice. The Panel noted Wyeth's submission that the prescribing decision of the GP had to be made in writing in advance of the offer of the service. The medication review booklet (ref ZZOT3587) explained that the Gastrocare service was available to review any oral PPI dose at the request of the practice. The representatives' 'Action plan: Gastrocare service offerings' explained that if the GP chose to change from one formulation of a PPI medication to another in a dose for dose switch, the most suitable service was the GP System Specialist Implementation. If any other change was required, or if the GP did not wish for this service, the GP was offered the Gastrocare Audit Review.

The Panel noted that representatives were instructed that all practices signed up under the withdrawn FBI service must be re-signed under the new service. The regional business managers had been told why the previous service was withdrawn and instructed the representatives in relation to the revised service. Representatives had to confirm that documentation in relation to the original service was returned to head office or destroyed locally.

The Panel noted Wyeth's submission that the complainant had requested a review of his PPI prescribing from Zoton to Zoton FasTab and had informed the representative at the outset that this prescribing decision had been agreed with the relevant PCT. The Panel also noted Wyeth's submission that the medication review spreadsheet was completed and signed before any service offerings were discussed.

The booklet GP Systems Specialist Implementation Pack (ref ZZOT3585) explained the role of the GP Systems Specialist in relation to the implementation of the GP prescribing requests as set out in the medication review spreadsheet. Wyeth submitted that this was the procedure to be implemented in the complainant's practice. No details were provided about the alternative service, the Gastrocare audit review. The Panel noted, however, that it was not the subject of complaint.

The Panel considered the arrangements only in relation to the alleged breach of undertaking. It did not consider the arrangements in relation to the requirements of Clause 18.1 as it had no complaint in that regard. The Panel considered that the service at issue was sufficiently different from that considered in Case AUTH/1561/3/04; the service was no longer restricted to switches from Zoton capsules to Zoton FasTab but was available for all oral PPIs. The Panel considered there was no breach of the undertaking previously given. The Panel had therefore ruled no breach of Clause 22. It thus followed there had been no breach of Clauses 9.1 or 2.

Case AUTH/1617/8/04

The Panel noted Wyeth's submission that the material and service offering at issue in the present case were the same as those considered in Case AUTH/1606/7/04. The Panel thus considered that its ruling in Case AUTH/1606/7/04 applied here. No breach of Clauses 22, 9.1 and 2 was thus ruled.

The Panel noted that a separate case, Case AUTH/1652/11/04, concerned the role of the representative in relation to the revised service.

In relation to the allegation that the long-term financial penalty of switching patients was misrepresented, the Panel noted Wyeth's submission that the position was very complicated and could not be identified with certainty. The Panel also noted Wyeth's submission that the representatives were careful to include appropriate caveats reflective of the speculative nature of the discussion.

The Panel considered that, irrespective of any caveats applied by the representatives, supposition was not a reasonable basis upon which to make promotional claims and had the potential to mislead. The Panel considered the discussion about the long-term financial consequences of switching was misleading. A breach of Clause 7.2 was ruled. The representatives had not maintained a high standard; a breach of Clause 15.2 was ruled.

Complaint received **10 August 2004**

Case completed **14 February 2005**

CASE AUTH/1626/8/04

PRIMARY CARE TRUST PHARMACIST v GLAXOSMITHKLINE

Implementation of a service

A senior practice pharmacist at a primary care trust (PCT) complained about the 'Airways Integrated Management Service' (AIMS) sponsored by Allen & Hanburys. The complainant referred to a letter about the service and the implementation of the service in a local GP practice.

The service was provided via an independent nursing agency and the purpose appeared to be to transfer patients from an inhaled corticosteroid and a long acting beta-agonist inhaler to Seretide.

The complainant believed that the letter contained misleading or irrelevant claims about the benefits of the service. It was claimed that an average GP practice could save £9,789 by implementing the recommended changes. The complainant had asked how this sum was calculated but had yet to receive an answer.

The claim for benefit to patients of improved control and compliance through the switch to a combination inhaler could not be justified; the British Thoracic Society Guideline on the management of asthma stated that combination inhalers had not been shown to improve compliance (with prophylactic asthma medication) in the medium to long term.

The complainant noted that the fact that there would only be one prescription charge payable would be largely irrelevant to patients at her practice. The issue of one dispensing fee was irrelevant as far as the practice was concerned.

With regard to the implementation of the service, the complainant listed a number of what she considered were inappropriate therapy recommendations made by the agency nurse. The complainant considered that these recommendations represented poor practice. She believed that the whole AIMS service breached the Code and should be withdrawn. Allen & Hanburys was sponsoring a nurse to review patient medication and using the service to induce the prescription of Seretide.

The Panel noted that the complainant had referred to AIMS in relation to both a letter and the implementation of a service at a GP practice. The letter referred to AIMS but GlaxoSmithKline had explained that the Asthma Patient Review Service (APRS) not AIMS was implemented in the practice in question.

The Panel noted that the AIMS service would provide either a person from an IT company or reimbursement to the practice to undertake its own review. Part of the complaint was about the provision of an asthma nurse service – such provision was part of APRS and not AIMS. The position was confusing as the letter at issue referred to the AIMS service.

The Panel noted that AIMS and APRS were considered in Case AUTH/1597/6/04.

In Case AUTH/1597/6/04 the Panel noted that the Airways Integrated Management Service (AIMS) was introduced to health professionals by the AIMS representative. The AIMS detail aid bore prescribing information for, *inter alia*, Seretide and some pages bore the Seretide product logo. The detail aid referred to the Gaining Optimal Asthma Control (GOAL) study in which '44% of Seretide patients achieved total control'. One page, headed 'Say no to separate inhalers', featured a photograph which showed that a Serevent inhaler plus a Becotide 100 inhaler were equal to a Seretide inhaler. The Panel considered that the service was part of the promotion of Seretide and other GlaxoSmithKline products; it was not described as anything else in the material.

The detail aid explained how AIMS worked. Under a heading of 'What Next?' step 1 was given as 'Decide which of your patients or groups you want to convert to Seretide …'. Doctors were told that the transfer of patients could be done, free of charge, by a third party, or by the practice staff sponsored at £15/hour for up to 15 hours. In a practice of 3 GPs and 4,500 patients, the typical cost savings would be £9,789. The service would thus benefit a practice in two ways, by saving it the expense of carrying out the switch itself and by saving it prescribing costs. The arrangements as described in the detail aid amounted to a pecuniary advantage given as an inducement to prescribe Seretide. The Panel thus ruled a breach of the Code. High standards had not been maintained and a breach of the Code was ruled. The Panel noted that the representatives had offered the service but had not been involved in changing prescriptions; this had been carried out by a third party on behalf of GlaxoSmithKline or by the practice. The Panel had thus ruled no breach of the Code. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code.

With regard to the asthma patient review service (APRS), the Panel noted that respiratory care associates (RCAs) introduced the service to health professionals although introductory letters could be sent by the Seretide representative. The APRS detail aid did not refer to any medicines by brand or generic name; only medicine classes were mentioned ie corticosteroids or bronchodilators. The first few pages of the APRS detail aid were very similar to the first few pages of the AIMS detail aid. One page, headed 'You can achieve total control in almost half your patients', discussed the results of the GOAL study. A bar chart depicted 44% of patients on combination achieving total control in GOAL. The combination product was Seretide although this was not stated. The APRS leavepiece stated that the landmark GOAL study had redefined the aims of asthma management and established a new composite outcome measure of 'Total Control'. Total control was defined and it was stated that aiming for

it should benefit all patients. At the foot of the leavepiece it was stated that Allen & Hanburys might be able to help practices review their asthma patients.

The Asthma Patient Review Programme Folder appeared to be for GP practices. It set out the patient review protocol including identification of inadequately controlled asthma patients. The therapy recommendation form stated that unless there was a clear therapeutic reason for change the following principles would apply: the delivery device would remain unchanged, wherever possible molecule consistency would be maintained and any changes should avoid increasing the complexity of the treatment regime where possible.

The asthma training manual for the agency nurses involved in delivering the APRS stated that the aims and objectives of the service were 'To provide an independent Nurse service to Primary and Secondary care in order to enhance and improve the quality of life and severity of disease for Patients with Asthma through improved Patient management, following the guidance of the BTS/SIGN Guidelines 2003'. There was general information on the anatomy, physiology and epidemiology of asthma together with information about asthma and daily life and a detailed discussion of all of the devices available for treatment. It was stated that the GP had prescribing responsibility and that GPs must authorize all recommendations. The agency nurses were told that at no time could they change prescription information on the computer or print any prescriptions off in support of their clinical recommendations. The need to have all documentation complete and signed was stressed.

Overall, the Panel considered that the APRS was not unacceptable; it would benefit the NHS and enhance patient care. Provision of the service was not linked to the prescription of any specific medicine. The decision of what, if anything, to prescribe lay with the doctor. The Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breaches of the Code had been ruled.

The Panel noted that GlaxoSmithKline had provided the requisite undertaking and assurance with regard to the Panel's ruling in relation to the AIMS service in Case AUTH/1597/6/04. The complainant had not appealed the Panel's rulings of no breach of the Code.

In the present case, Case AUTH/1626/8/04, the Panel noted GlaxoSmithKline's explanation that the 'Dear Practice' letter at issue was created and distributed by the representative without head office approval.

The complainant had not received a response to the enquiry as to how the claim 'Cost savings: based on national GP database information an average GP practice could save an estimated £9,789 per year' had been calculated. Substantiation had not been provided without delay at the request of a health professional. A breach of the Code was ruled.

The Panel noted that the claim 'Improved control and compliance' was described as one of a number of benefits which AIMS could provide for both patients and the practice. The Panel noted that AIMS was described as helping to 'transfer asthma patients receiving concurrent ICS [inhaled corticosteroids] and LABA [long-acting beta-agonists] to a therapeutically equivalent combination formulation eg. Seretide…'. The Panel noted the complainant's submission that combination inhalers had not been shown to improve compliance (with prophylactic asthma medication) in the medium to long term. The Panel noted GlaxoSmithKline's comments on McCarthy *et al* (2002) and (2003) in relation to compliance and asthma control and Seretide. The Panel considered that the claim in the letter for improved compliance and asthma control would be read as a benefit attributable to both ICS/LABA combination inhalers; not just Seretide. The Panel noted that no substantiation had been submitted in this regard although there was data to support the claim for Seretide. The Panel considered the claim 'Improved control and compliance' within the context of the letter at issue was misleading and not capable of substantiation; a breach of the Code was ruled.

In relation to the claim 'Patients only have to pay one prescription charge and the NHS has to pay for one dispensing fee' the Panel noted that the patient populations of practices would vary. The letter was not designed to address the circumstances of each individual practice. The letter was not misleading on this point; no breach of the Code was ruled. The Panel did not consider that the 'Dear Practice' letter warranted a breach of Clause 2.

The rulings about the 'Dear Practice' letter were not appealed by either party.

The Panel noted that APRS, not AIMS, had been implemented at the practice in question. The Panel considered that its comments on the APRS documentation asthma training manual and role of the independent nurse in Case AUTH/1597/6/04 were relevant here.

The Panel noted the gravity of the complainant's allegations about the recommendations made by the sponsored nurse at the practice in question. Further the Panel noted GlaxoSmithKline's submission that it was satisfied the protocol was followed. GP signatures were obtained at all stages of the service including therapy recommendations. All recommendations made by the nurse adviser were within the remits of the protocol approved by the practice. No therapy recommendations were made in 15 of the 29 patients reviewed. Further, the practice did not implement any of the therapy recommendations suggested. GlaxoSmithKline had not had access to patient details.

The Panel considered that without more details of the protocol agreed in the practice it was impossible to make a judgement on the complainant's specific criticisms. The standard protocol clearly stated that unless there was a clear therapeutic reason for change the delivery device would remain unchanged, wherever possible molecule consistency would be maintained and any changes should avoid increasing the complexity of treatment regime where

possible. The protocol excluded patients with COPD (chronic obstructive pulmonary disease). The therapy recommendation form to be completed by a practice GP and the APMS nurse advisor set out various treatment regimens and suggested recommendations to be made by the nurse advisor. The GP was to initial each recommendation. In relation to patients with confirmed diagnosis or indication by symptoms of COPD the nurse advisor was to refer such patients to the GP or practice nurse as decided by the GP completing the form. The nurse advisor clinic process included an assessment of inhaler technique and compliance. The Panel also noted its previous ruling in Case AUTH/1597/6/04 that overall the APRS was not in breach of the Code. On balance on the limited evidence before it the Panel considered that the APRS, as implemented in the practice in question, was not in breach of the Code and thus no breach was ruled. The Panel thus also ruled no breach of Clause 2 of the Code in this regard.

The complainant appealed the Panel's rulings with regard to the implementation of the service whereupon the Appeal Board noted GlaxoSmithKline's submission that it was satisfied the protocol was followed and that the complaint revolved around a difference in clinical opinion. GP signatures were obtained at all stages of the service including therapy recommendations. No therapy recommendations were made in 15 of the 29 patients reviewed. Further, the practice did not implement any of the therapy recommendations suggested. The Appeal Board noted the complainant's submission on this point.

The Appeal Board was concerned about the gravity of the complainant's allegations with respect to the recommendations made by the sponsored nurse at the practice in question and noted that extreme dissatisfaction was normally necessary on the part of a health professional before he/she was moved to submit a complaint. GlaxoSmithKline had submitted that it had no access and hence no knowledge of the individual cases in question. The Appeal Board did not know the details of each patient's case and it considered that without these it was impossible to make a judgement on the specific criticisms raised by the complainant.

The Appeal Board noted the complainant's comments about the recommendations made by the sponsored nurse in relation to COPD patients. The Appeal Board noted that it did not have the protocol agreed in the practice before it. The complainant stated that the protocol agreed with the practice was the standard protocol as in the documentation with one change to include the option of the nurse discussing medication issues with the practice pharmacist. Notwithstanding the wisdom of any of the recommendations made by the sponsored nurse with respect to specific patients, the Appeal Board noted that none of them had been implemented and that the GPs in the practice had made the final decisions about individual patient management. The protocol was thus robust in that regard. The Appeal Board noted the Panel's previous ruling in Case AUTH/1597/6/04 that overall the APRS was not in breach of the Code. On the limited evidence before it the Appeal Board considered that it had no option other than to uphold the Panel's rulings that the APRS as implemented in the practice in question was not in breach of the Code. The Appeal Board thus also considered that the implementation of APRS in the practice in question did not warrant a ruling of a breach of Clause 2 which was reserved to indicate particular censure. The Appeal Board upheld the Panel's ruling of no breach of Clause 2.

A senior practice pharmacist at a primary care trust complained about a service sponsored by Allen & Hanburys, part of GlaxoSmithKline UK Ltd. The complainant referred to a letter (ref SFL/LTR/03/08321/1-June 2003) about the service and the implementation of the service in a local general practitioner practice.

COMPLAINT

The complainant alleged that the provision of an asthma nurse service to one of her local GP practices appeared to contravene Clauses 7 and 18.1 of the Code.

The service was provided by an agency, supported by a grant from Allen & Hanburys, and was known as the 'Airways Integrated Management Service' (AIMS). The purpose appeared to be to transfer patients from an inhaled corticosteroid and a long acting beta-agonist inhaler to a combination product.

Allen & Hanburys had provided misleading information on the supposed benefits of the service. There had been cases of inappropriate recommendations being made about individual patients' treatment, and the service appeared to be a financial inducement to prescribe a particular medicine.

The complainant believed that the letter, which was signed by the local representative contained misleading or irrelevant claims about the benefits of the service. In the letter it was claimed that an average GP practice could save £9,789 by implementing the recommended changes. The complainant had telephoned the representative on 5 August to ask for a breakdown of these projected savings. The representative responded by asking the complainant for information about the current situation in the practice so that his answer could be more specific, and he intimated that most practices were able to save around £3,000-£4,000 in reality. The complainant pointed out that she was just looking for the calculation on which the £9,789 was based and he then agreed to find that information for her. The complainant had yet to receive it. A breach of Clause 7.5 of the Code was alleged.

The claim for benefit to patients of improved control and compliance through the switch to a combination inhaler could not be justified as according to the British Thoracic Society Guideline on the management of asthma, combination inhalers had not been shown to improve compliance (with prophylactic asthma medication) in the medium to long term.

The complainant noted that the fact that there would only be one prescription charge payable would be largely irrelevant to her practice, as it was located in

an area of high social deprivation where very few patients paid prescription charges. The issue of the one dispensing fee was irrelevant as far as the practice and the patients were concerned.

The complainant listed the inappropriate recommendations for change of therapy that had been recommended by the asthma nurse employed to manage the AIMS process.

1 The doctors had agreed that the switch to combination inhalers could be to either Serevent or Symbicort, but up until now all recommendations for combination inhalers had been for a 'combination metered dose inhaler' which implied Serevent, or for an Accuhaler, thus eliminating the possibility of prescribing Symbicort.

2 A patient diagnosed by the nurse as possibly having COPD and requiring spirometry, was also recommended to be switched from beclometasone inhaler 250mcg 2 puffs twice a day and salmeterol inhaler 25mcg, 2 puffs twice a day to 'combination metered dose inhaler 250'. This involved doubling the steroid dose, assuming that 2 puffs twice a day of Seretide were to be prescribed to achieve the recommended dose of salmeterol. The complainant considered that the outcome of the spirometry investigation should be taken into consideration before any increase in the dose of inhaled steroid, as steroid treatment might not be appropriate for this patient.

3 A patient on Becodisks and Ventodisks was diagnosed as being uncontrolled, but no check was made on compliance with the Becodisks, by prescription collection rate, which was found to be less than 50%. Therefore, the recommendation to switch to a Seretide Accuhaler which would involve adding in a long-acting beta agonist was inappropriate until the patient had been educated in technique and his poor compliance with steroid therapy had been addressed.

4 In the cases of several other patients switches to a combination metered dose inhaler, which involved the addition of a long acting $beta_2$ agonist, were recommended without patient compliance with their steroid inhaler being addressed.

5 Other patients requiring spirometry for possible COPD were recommended to receive a combination metered dose inhaler prior to a diagnosis being established.

6 A patient on Qvar and Airomir Autohalers was informed that he would need to change to a combination Accuhaler as these products were soon to be discontinued. A check with the manufacturer of products confirmed that this was not so.

7 The AIMS nurse advised one of the patients that she was using her Volumatic device incorrectly, contrary to advice previously given by the practice nurse. A check with Allen & Hanburys confirmed that either method was correct. The practice nurse was concerned to find that her advice was being undermined by a fellow health professional.

The complainant considered the events detailed above to be instances of poor practice. The complainant believed that the whole AIMS service breached Clause 18.1 of the Code and it should be withdrawn. Allen & Hanburys was sponsoring a service provider to review patient medication and then by suggesting to the general practitioner they prescribe, in effect, a specific medicine the company was inducing the prescription of a medicine.

The complainant noted that Wyeth had recently been ruled in breach of the same clause of the Code when sponsoring a service provider to change Zoton to Zoton FasTab. This service was very similar to AIMS and therefore the complainant believed AIMS breached the Code in the same way. Allen & Hanburys might argue it was not inducing the prescription of a specific medicine, since the GPs indicated beforehand which medicines they wished reviewed, which ones they wished to consider the patient was changed to, and the GP actually made any change. However, in practice this distinction was academic. The information for the GP to make this change if they wished had been provided through sponsorship, and in practice the vast majority of recommendations were worded such that Seretide was the only medicine that fitted, and often where prescription of Seretide was not a reasonable course of action. Therefore in practice Allen & Hanburys was sponsoring GPs to prescribe Seretide through AIMS.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 2 and 9.1 in addition to the clauses cited by the complainant.

RESPONSE

GlaxoSmithKline stated that AIMS and the agency were two distinct entities which were not connected. GlaxoSmithKline held a contract with the agency to provide independent specialist nurse advisers for the Asthma Patient Review Service (APRS), but not the AIMS service.

GlaxoSmithKline refuted the suggestion that any of the patient services it provided were in breach of the Code. All followed strict protocols and required full authorization at every stage by the practice involved. The final decision to implement any recommendations made during the provision of a service rested with the practice. Furthermore, these services had the potential to significantly enhance patient care and benefit the NHS.

1 The acceptability of AIMS in relation to Clause 18.1

AIMS evolved from a CFC-Transition Service and was designed to assist doctors transfer patients from an inhaled corticosteroid (ICS) and inhaled long acting $beta_2$-agonist (LABA) to a therapeutically equivalent combination if the doctor considered that to be the most appropriate course of action. Doctors were not obliged to transfer patients onto a specific inhaler. The overarching theme of the AIMS programme was about potential benefit for both the patients and the practice:

- Simplified treatment using a single inhaler

- Improved control and compliance
- Cost savings: based on national GP database information, an average GP practice could save an estimated £9,789 per year. Patients paid one prescription charge and the NHS paid one dispensing fee
- CFC-free transition.

Process

AIMS was promoted, but not delivered, by a team of sixty dedicated AIMS representatives. This was a promotional sales force. Doctors might be introduced to the concept of AIMS either via the AIMS representative or via a letter of introduction outlining the programme.

- The practice decided which patient types they wished to review and authorized this decision.
- Either a specialist independent IT company or practice staff (nurse, doctor, pharmacist or manager) searched for patients fulfilling selection criteria on the practice computer to produce a list. This process was authorized by the doctor/s.
- This list was reviewed by the doctor/s, who then decided an appropriate course of action. This might include a therapy change or an invitation to attend for an asthma review. This activity was solely agreed and authorized by the doctor/s. Patient information remained confidential and was retained within the practice.
- The prescribing database was updated either by the IT company or practice staff.
- For those patients for whom a therapy change was made without asthma review, a letter of notification, customised by the practice was sent, along with a patient feedback card.

Implementation

If the practice decided to proceed with the AIMS programme, it might do so either by using the IT company or practice staff.

Via the IT company

- The AIMS Authorization Form was completed at the time of agreement to the service. At this point the GP authorized the file search to identify patients who might be suitable for a therapy transfer. The choice of patients and search criteria used were entirely the doctor's decision. This file search required two GP signatories. A written undertaking to ensure transparency of communication within the practice was required. Written authorization by two GP signatories to conduct a computer search of patients currently prescribed an inhaled LABA together with an ICS via metered dose or dry powder inhalers was required. The facilitator from the IT company must give a written undertaking of confidentiality. A medication list for the file search was determined, which also required written authorization by a GP.
- The GP reviewed the list of patients generated by the file search, and identified those whom he wished to review in person. The GP authorized the facilitator from the IT company to make the repeat medication changes on the prescribing database. This review and authorization was confirmed on the authorization form by the GP.
- Patients were informed of the planned change or invited to make an appointment for an asthma review via a letter from the practice. Sample letters were provided in the patient sample letter pack, which might be customised by the practice, as appropriate. A patient feedback card was included with those letters notifying a planned transfer of therapy.
- Final sign-off for completion of the AIMS programme was given only when the practice was satisfied that all stages of the review process had been carried out in accordance with the agreed procedures.
- Once completed, the authorization form was returned to the IT company by its facilitator.

Via Practice Staff

- The AIMS Application Form for Financial Support was used at the time of agreement to initiate the review, if the practice desired remuneration for practice time.
- The GP reviewed the list of patients generated by the file search, identified those whom he wished to review in person, and nominated a member of staff to complete repeat medication changes on the prescription database, according to written instructions given in the AIMS Authorization Form.
- Patients were informed of the planned change or invited to make an appointment for an asthma review via letter from the practice. Sample letters were provided in the patient sample letter pack, which might be customised by the practice, as appropriate. A patient feedback card was included with those letters notifying a planned transfer of therapy.
- Final sign-off for completion of the AIMS programme was given only when the practice was satisfied that all stages of the review process had been carried out in accordance with the agreed procedures. If the practice completed an application for funding, this was sent to or collected by the AIMS representative and the application was processed by GlaxoSmithKline.

As outlined above, the AIMS service was promoted but not delivered by AIMS representatives. Service delivery was implemented by either the practice staff or an independent IT company, and at no point did AIMS representatives handle information that could be linked to or identify patients. All services required full authorization by the GP at every stage who made the final decision regarding any therapy change. If a practice did not want help from the IT company there was an option of financial support, £15/hour up to maximum of 15 hours (£225) as reimbursement to the practice of time spent in implementing the process. GlaxoSmithKline did not believe that this payment could be misconstrued as an inducement to prescribe, and practices were not obliged to have the financial

support. GlaxoSmithKline strongly denied the complainant's assertion that the service appeared to be a financial inducement to prescribe a particular medicine.

GlaxoSmithKline firmly believed that the AIMS service was fully compliant with the requirements of the Code and denied any breach of Clause 18.1 or Clause 2.

2 'Dear Practice' letter

a) Misleading information on supposed benefits

As indicated above, doctors might be introduced to the concept of AIMS either via the AIMS representative or via a letter, outlining the AIMS programme.

GlaxoSmithKline noted that the complainant had alleged that the claim 'Improved control and compliance' could not be justified.

The BTS/SIGN Asthma Guideline had confirmed that prescription counting and computerised repeat prescribing systems provided useful methods of assessing compliance with prescribed medication. Furthermore, the use of short acting beta$_2$-agonist medication (SABA) was well recognised as an important marker of asthma control. McCarthy *et al* (2002) and (2003) had examined data from DINLINK, a GP database prescribing system, and these data had confirmed that the use of Seretide was associated with significantly improved compliance when measured against separate inhalers of ICS and LABA. Seretide was associated with a compliance rate approaching the ideal of 1/month more closely than the other regular asthma medications as separate inhalers. The data also demonstrated that the use of Seretide was associated with significantly improved asthma control, measured as the number of SABA prescriptions, compared with using separate inhalers. These data applied to both children and adults.

Where control and compliance were management issues, Seretide was a rational choice as it was a combination therapy, which had been shown to have control and compliance benefits over its component parts given concurrently or separately.

GlaxoSmithKline maintained that the claim of improved control and compliance could be substantiated and denied a breach of Clause 7.4.

GlaxoSmithKline noted that the complainant had requested substantiation for the claim that 'Cost savings: based on national GP database information, an average GP practice could save an estimated £9,789 per year'. This cost saving was provided to the practice as an example of what it might save. If the practice expressed an interest in the service, the AIMS representative could calculate a more detailed potential cost saving based upon specific data provided to them from the practice.

The average cost saving was calculated as follows:

- An average GP practice consisted of three GPs and 4,500 patients;
- The estimated household prevalence of asthma amongst the screened population in the UK was 14.8%;
- 4,500 x 14.8% = 666 patients with asthma in an average practice;
- 69.2% of patients with asthma were on an inhaled steroid, therefore, 666 x 69.2% = 461 patients were on an inhaled corticosteroid;
- 18.1% of asthma patients on an inhaled steroid also received a LABA, therefore, 461 x 18.1% = 83 patients on an ICS + LABA.

Prescribing data showed patients with asthma on both an inhaled steroid and salmeterol. For accuracy these data had been scaled up to show the breakdown for 1000 patients.

Cost calculations had been based on the ICS + LABA combinations listed in the cost calculator.

- The typical savings were calculated for 1000 patients, by comparing the cost of separates with the cost of Seretide as a combination inhaler = £117,944.
- This figure was then scaled down to 83 patients: therefore, typical savings of £117,944 x 83/1000 = £9,789 for 83 patients within an average GP practice.

GlaxoSmithKline maintained that the claim of potential savings for an average GP practice could be substantiated and denied a breach of Clause 7.4.

b) Approval of letter

GlaxoSmithKline acknowledged that the letter issued by the AIMS representative on this occasion was not head office approved. Although there were no factual inaccuracies contained within the letter, it appeared that the representative generated the letter from a previously approved head-office post-call mailing. GlaxoSmithKline required all pre-call and post-call mailings to be approved. Any requests for *ad hoc* mailings from representatives should be sent into head-office, where they were reviewed for approval. On this occasion the process was not followed, an *ad hoc* mailing was issued without head-office approval and GlaxoSmithKline accepted that it was in breach of Clause 9.1 since high standards were not maintained.

The representative was suspended immediately it became apparent that the letter had not been approved by head office. He was currently subject to a disciplinary review in accordance with GlaxoSmithKline's policies and procedures.

GlaxoSmithKline noted the complainant's assertion that the claim 'Patients only have to pay one prescription charge; the NHS has to pay for one dispensing fee' was irrelevant. The company submitted that the standard approved mailings had been designed to highlight the potential benefits to an average practice. By using a combination inhaler, patients normally only paid one prescription charge and the NHS incurred only one dispensing fee. Clearly patients' individual circumstances varied and so this might not always be relevant for all patients within all practices. The letter was designed for average practices and the details of potential benefits for individual practices could be discussed in more

detail by the AIMS representative at subsequent interview.

c) Timing of response for information

The day after the AIMS representative received the request from the complainant for information regarding the potential cost savings the representative tried to contact an AIMS manager, who was unavailable at the time of his call, so a message was left. The AIMS manager did not fully understand the detail of the request nor the urgency of response required. Unfortunately the representative left on annual leave the next day and was unable to discuss fully the detail and urgency of the request with the manager. As a result, although unintentional, GlaxoSmithKline failed to respond to the complainant's request without delay, contrary to the company's policies and procedures. GlaxoSmithKline accepted that on this occasion, it was in breach of Clause 7.5. Both the representative and the manager had been subject to a disciplinary review.

3 Conduct of the switch programme within the practice involved

GlaxoSmithKline noted that no activity was undertaken at the complainant's practice as part of the AIMS service offered. However, it appeared that the complainant was referring to the Asthma Patient Review Service (APRS), which was delivered through the independent agency.

APRS and associated protocols

The APRS was a non-promotional patient audit initiative. It was introduced and arranged with participating practices via the GlaxoSmithKline Respiratory Care Associate (RCA) but delivered through either the independent agency or the practice. The aim of the asthma patient reviews was to help practices review their poorly controlled patients, as defined by the practice itself. The patients were reviewed by either the agency nurse or the practice nurse who, with the permission of the practice, checked various aspects of patient treatment and recommended changes to patient management as appropriate to their clinical condition. Signed consent from the practice was obtained at every step.

GlaxoSmithKline had reviewed the protocol and believed it to be appropriate and consistent with the supplementary information detailed in Clause 18.1.

- The audit was intended to improve patient care.
- There was no condition regarding treatment choice applying (ie there was no product bias).
- The project did not bear the trademark of any medicine.
- The nurses performing the audit were not employed by GlaxoSmithKline; they were employed and trained by the agency in accordance with operating procedures agreed with GlaxoSmithKline.
- Neither the RCA nor the agency nurse were involved with promotion or promotional material.
- The nurses performing the audits were appropriately experienced, qualified and professionally registered.
- Only the nurse had any access to patient records.
- Patient confidentiality was maintained and appropriate consent sought from the practice.
- The nurses' remuneration was not linked to any sales figures or treatment changes.
- Detailed contracts, operating procedures and training manuals had been agreed that identified the role of the nurses and which stated that GP consent must be obtained to therapy changes. Further these instructions did not advocate any course of action which would be likely to lead to a breach of the Code.
- There was no attempt to disguise GlaxoSmithKline sponsorship.
- Written protocols were given to the practice and signed consent obtained at every step.
- No promotional materials were used as part of the audit.
- All briefing materials, contracts and training materials and protocols had been approved by signatories in accordance with company standard operating procedures.

Training of GlaxoSmithKline personnel and agency personnel

General

Both GlaxoSmithKline and agency personnel received appropriate training regarding the non-promotional nature of their role, and the protocols and procedures to be followed.

Training the AIMS representative:

The representative had undergone the appropriate ABPI Code of Practice training, and had undergone his most recent GlaxoSmithKline internal training update in May 2004. GlaxoSmithKline was satisfied that the representative was appropriately trained, experienced and registered in accordance with GlaxoSmithKline and ABPI requirements. As mentioned above, on this occasion its representative did not act in accordance with GlaxoSmithKline policies and procedures and it accepted that his behaviour constituted a breach of Clause 9.1 since high standards were not maintained.

The training of the agency nurse:

The complainant had highlighted several inappropriate recommendations for change of therapy, which were made by the asthma nurse involved, commenting that she considered these to be poor practice.

GlaxoSmithKline was unable to comment on the specific details of the cases highlighted in the complainant's letter. The APRS service protocol and the Code prohibited GlaxoSmithKline employees from handling confidential information about patients without consent. Without this information and a clear understanding of the clinical issues involved with these patients, GlaxoSmithKline considered it inappropriate to comment on the clinical decisions of an independent health professional.

However, GlaxoSmithKline had reviewed the agency service provided within the practice in question, to determine whether all actions taken by the nurse were within the protocols. GlaxoSmithKline was satisfied that the protocol was followed and specifically that all consent forms including therapy recommendations were approved and signed by the GPs within the practice.

All relevant GP signatures within the practice in question were obtained at all stages of the service. All recommendations made by the independent nurse adviser were within the remits of the protocol approved by the practice. GlaxoSmithKline noted that of 29 patients reviewed, no therapy recommendations were made in 15 of them. Furthermore, the practice did not implement any therapy recommendations suggested, highlighting that the ultimate decision to change any patients' treatments lay with the practice GPs.

Conclusion

As stated above, GlaxoSmithKline accepted that there had been a breach of Clauses 7.5 and 9.1 of the Code by the actions of the AIMS representative in issuing a non-approved letter, and by both the agency representative and the manager in failing to respond to a query in good time. Both the representative and the manager had been subject to a GlaxoSmithKline disciplinary review.

In all other respects however, GlaxoSmithKline was confident that the services referred to complied with the Code and refuted all allegations of any breaches of Clauses 18.1 or 2. It firmly believed that both the theme and content of the AIMS and APRS programmes complied with the letter and spirit of the Code, and provided a service to medicine. GlaxoSmithKline denied any breach of Clause 2 since it considered that the manner of the AIMS programme itself was not implicated by its representative's actions, and the overall operation of AIMS was well regulated and within strict protocols.

PANEL RULING

The Panel noted that the complainant had referred to AIMS in relation to both the 'Dear Practice' letter and the implementation of a service at a local GP practice. The 'Dear Practice' letter supplied by the complainant referred to AIMS; it did not refer to APRS. GlaxoSmithKline had explained that APRS not AIMS was implemented in the practice in question.

The Panel noted that the AIMS service would provide either a person from an IT company or reimbursement to the practice to undertake its own review. Part of the complaint was about the provision of an asthma nurse service – such provision was part of APRS and not AIMS. The position was confusing as the letter at issue referred to the AIMS service.

The Panel noted that AIMS and APRS were considered in Case AUTH/1597/6/04. The Panel's ruling was as follows:

Panel ruling in Case AUTH/1597/6/04

The Panel decided to consider each service separately. The Panel did not dispute that changes in medication might significantly impact on patients' lives for many reasons. However all arrangements had to comply with the Code.

1 AIMS

The Panel noted that the AIMS representative introduced the service to health professionals. AIMS was clearly linked to the promotion of Seretide. The AIMS detail aid (ref 20528422 SFL/DAP/04/11347/1 – FP/March 2004) used to describe the service to health professionals bore prescribing information for Seretide, Flixotide, Serevent, Becotide (beclometasone) and Becloforte (high dose beclometasone) on the back page. Pages 4, 5 and 6 each bore the Seretide product logo. The detail aid referred to the GOAL study in which '44% of Seretide patients achieved total control'. Page 5 of the detail aid was headed 'Say no to separate inhalers' and featured a photograph which showed that a Serevent inhaler plus a Becotide 100 inhaler were equal to a Seretide inhaler. The detail aid explained how AIMS worked. Under a heading of 'What Next?' step 1 was given as 'Decide which of your patients or groups you want to convert to Seretide …'. Doctors were told that the transfer of patients could be done, free of charge, by an independent IT company or by the practice staff sponsored at £15/hour for up to 15 hours. Page 6 of the detail aid stated that in a practice of 3 GPs and 4,500 patients, the typical cost savings would be £9,789.

The Panel considered that the service was part of the promotion of Seretide and other GlaxoSmithKline products; it was not described as anything else in the material. The service could thus not benefit from the supplementary information to Clause 18.1 regarding the provision of medical and educational goods and services.

The application for financial support (ref SFL/ATF/04/11967/120549613 – FP/March 2004) referred to rationalisation of long-acting ß2 agonist and inhaled corticosteroid therapy. The suggested search included patients on salmeterol or formoterol (AstraZeneca or Novartis) plus inhaled corticosteroids marketed by Baker Norton, 3M, AstraZeneca, Trinity and Celltech as well as GlaxoSmithKline products.

Switching patients to Seretide might be a less expensive way of prescribing Serevent and Becotide. Companies could of course promote products on the basis of cost and it was not unreasonable to note savings that a practice might make by switching from one product to another. The difficulty was when the company paid directly or indirectly for those changes to be made because then the company's actions amounted to it paying to boost the prescription of a specific medicine. In this regard the Panel noted that the AIMS detail aid recommended using AIMS to switch patients to Seretide. The service was promoted by representatives. Although other materials were more general and did not refer to switching patients to Seretide the Panel nonetheless noted that Clause 18.1 of the Code stated that 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe,

supply, administer, recommend or buy any medicine, subject to the provisions of Clause 18.2'. AIMS was introduced to GPs via the detail aid as a service to help them switch patients to Seretide and in doing so save on prescribing costs. The service would thus benefit a practice in two ways, by saving it the expense of carrying out the switch itself and by saving it prescribing costs. The arrangements as described in the detail aid amounted to a pecuniary advantage given as an inducement to prescribe Seretide. The Panel thus ruled a breach of Clause 18.1 of the Code. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel noted that the representatives had offered the service but had not been involved in changing prescriptions; this had been carried out by a third party on behalf of GlaxoSmithKline or by the practice. The Panel thus ruled no breach of Clause 15.2. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a mark of particular censure and thus no breach of Clause 2 was ruled.

During its consideration of this aspect the Panel noted that there did not appear to be up-to-date instructions to representatives. Copies of briefing documents for the CFC service were provided but these were dated 2001. No briefing material on AIMS had been provided.

2 APRS

The Panel noted that RCAs introduced the service to health professionals although introductory letters could be sent by the Seretide representative. The APRS detail aid (ref SFL/DAP/04/11902/1-FP/March 2004) did not refer to any medicines by brand or generic name; only medicine classes were mentioned ie corticosteroids or bronchodilators. The first few pages of the APRS detail aid were very similar to the first few pages of the AIMS detail aid. Page 5 was headed 'You can achieve total control in almost half your patients' and discussed the results of the GOAL study. A bar chart depicted 44% of patients on combination achieving total control in GOAL. The combination product was Seretide although this was not stated. The APRS leavepiece (ref SFL/LVP/04/11440/1) stated that a landmark study, the Gaining Optimal Asthma Control (GOAL) study had redefined the aims of asthma management and established a new composite outcome measure of 'Total Control'. Total control was defined and it was stated that aiming for it should benefit all patients. At the foot of the leavepiece it was stated that Allen & Hanburys might be able to help practices review their asthma patients.

The agency Asthma Patient Review Programme Folder appeared to be a folder for GP practices. It set out the patient review protocol including identification of a target group of asthma patients whose asthma was not well controlled. The therapy recommendation form stated that unless there was a clear therapeutic reason for change the following principles would apply; the delivery device would remain unchanged, wherever possible molecule consistency would be maintained and any changes should avoid increasing the complexity of the treatment regime where possible.

The agency asthma training manual described the aims and objectives of the APRS as 'To provide an independent Nurse service to Primary and Secondary care in order to enhance and improve the quality of life and severity of disease for Patients with Asthma through improved Patient management, following the guidance of the BTS/SIGN Guidelines 2003'. There was general information on the anatomy, physiology and epidemiology of asthma together with information about asthma and daily life and a detailed discussion of all of the devices available for treatment. In a section detailing the aims and objectives of the service it was stated that the GP had prescribing responsibility and that GPs must authorize all recommendations. The agency nurses were told that at no time could they change prescription information on the computer or print any prescriptions off in support of their clinical recommendations. The need to have all documentation complete and signed was stressed.

Overall, the Panel considered that the APRS was not unacceptable in relation to the requirements of Clause 18.1; it would benefit the NHS and enhance patient care. Provision of the service was not linked to the prescription of any specific medicine. The decision of what, if anything, to prescribe lay with the doctor. The Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breach of Clause 18.1 of the Code was ruled. The Panel also ruled no breach of Clauses 2, 9.1 and 15.2 of the Code.

* * * * *

The Panel noted that GlaxoSmithKline had provided the requisite undertaking and assurance with regard to the Panel's ruling in relation to the AIMS service in Case AUTH/1597/6/04. The complainant had not appealed the Panel's rulings of no breach of the Code.

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Case AUTH/1626/8/04

In relation to the 'Dear Practice' letter the Panel noted that a similar letter had been provided by GlaxoSmithKline as part of its response to the previous complaint; it had not however been the subject of complaint *per se*. The Panel noted GlaxoSmithKline's explanation that the 'Dear Practice' letter at issue was created and distributed by the representative without head office approval.

The Panel noted that the complainant had telephoned the representative on 5 August to ask how the claim 'Cost savings: based on national GP database information an average GP practice could save an estimated £9,789 per year' had been calculated. The complainant had not received a response. Substantiation had not been provided without delay at the request of a health professional as required by Clause 7.5. A breach of Clause 7.5 was ruled. This ruling was not appealed.

The Panel noted that the claim 'Improved control and compliance' was described as one of a number of benefits which AIMS could provide for both patients

and the practice. The Panel noted that AIMS was described as helping to 'transfer asthma patients receiving concurrent ICS and LABA to a therapeutically equivalent combination formulation eg. Seretide…'. The Panel noted the complainant's submission that combination inhalers had not been shown to improve compliance (with prophylactic asthma medication) in the medium to long term. The Panel noted GlaxoSmithKline's comments on McCarthy *et al* (2002) and (2003) in relation to compliance and asthma control and Seretide. It also noted GlaxoSmithKline's submission that doctors were not obliged to transfer their patients onto a specific combination inhaler. Thus the Panel considered that the claim in the letter for improved compliance and asthma control would be read as a benefit attributable to both ICS/LABA combination inhalers; not just Seretide. The Panel noted that no substantiation had been submitted in this regard although there was data to support the claim for Seretide. The Panel considered the claim 'Improved control and compliance' within the context of the letter at issue was misleading and not capable of substantiation; breaches of Clauses 7.2 and 7.4 were ruled. These rulings were not appealed.

In relation to the claim 'Patients only have to pay one prescription charge and the NHS has to pay for one dispensing fee' the Panel noted the complainant's view that this was largely irrelevant as the GP practice at issue was located in an area of high social deprivation where very few patients paid prescription charges. The Panel noted that the patient populations of practices would vary and the claim would be relevant in some practices. The Panel noted GlaxoSmithKline's submission that the letter was designed for average practices. The letter was not designed to address the circumstances of each individual practice. The letter was not misleading on this point; no breach of Clause 7.2 was ruled. This ruling was not appealed.

During its consideration of the complaint about the 'Dear Practice' letter, the Panel noted its previous ruling regarding AIMS that it was clearly linked to switching patients to Seretide in breach of Clause 18.1 of the Code. GlaxoSmithKline had provided the requisite undertaking with regard to the Panel's rulings in Case AUTH/1597/6/04 in October 2004. In the Panel's view the linking of Seretide to the AIMS service in the 'Dear Practice' letter was covered by its ruling in Case AUTH/1597/6/04. The Panel requested that GlaxoSmithKline be advised of its concerns in this regard.

The Panel noted that APRS, not AIMS, had been implemented at the practice in question. The Panel considered that its comments on the APRS documentation asthma training manual and role of the independent nurse in Case AUTH/1597/6/04 were relevant here.

The Panel noted the gravity of the complainant's allegations about the recommendations made by the sponsored nurse at the practice in question. Further the Panel noted GlaxoSmithKline's submission that it was satisfied the protocol was followed. GP signatures were obtained at all stages of the service including therapy recommendations. All recommendations made by the nurse adviser were within the remits of the protocol approved by the practice. No therapy recommendations were made in 15 of the 29 patients reviewed. Further, the practice did not implement any of the therapy recommendations suggested. GlaxoSmithKline had not had access to patient details.

The Panel considered that without more details of the protocol agreed in the practice it was impossible to make a judgement on the specific criticisms raised by the complainant. The standard protocol clearly stated that unless there was a clear therapeutic reason for change the delivery device would remain unchanged, wherever possible molecule consistency would be maintained and any changes should avoid increasing the complexity of treatment regime where possible. The protocol excluded patients with COPD. The therapy recommendation form to be completed by a practice GP and the agency nurse advisor set out various treatment regimens and suggested recommendations to be made by nurse advisor. The GP was to initial each recommendation. In relation to patients with confirmed diagnosis or indication by symptoms of COPD the nurse advisor was to refer such patients to the GP or practice nurse as decided by the GP completing the form. The nurse advisor clinic process included an assessment of inhaler technique and compliance. The Panel also noted its previous ruling in Case AUTH/1597/6/04 that overall the APRS was not in breach of Clauses 18.1, 15.2, 9.1 and 2 of the Code. On balance on the limited evidence before it the Panel considered that the APRS, as implemented in the practice in question was not in breach of Clauses 18.1 or 9.1 of the Code and thus no breach of those clauses was ruled. These rulings were appealed.

The Panel considered that neither the 'Dear Practice' letter nor the implementation of APRS in the practice in question warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure. No breaches of Clause 2 were ruled. The ruling of no breach of Clause 2 with regard to the letter was not appealed. The ruling with regard to the implementation of ARPS in the practice in question was appealed.

APPEAL BY THE COMPLAINANT

The complainant was concerned that the Panel was of the opinion that the recommendations made by the agency nurse advisor for changes to the asthma treatment of patients involved in the programme were within the remits of the protocol approved by the practice, and contested that this was not the case.

The complainant considered that points 2 and 5 of her complaint were examples of poor practice, the nurse considered that the patients had a possible diagnosis of COPD. The protocol documentation of the APRS programme stated that patients with COPD must be excluded from the programme. Therefore, it would be expected that any patient who the nurse considered might have COPD would not have a change of medication until such time as spirometry had been carried out. Therefore, in the case of these two patients, the protocol was not adhered to.

In fact, the reason that none of the nurse's recommendations were acted upon by the GPs was because they were all considered to be inappropriate. Had the GPs and the complainant not been as vigilant in their monitoring of these recommendations, the patients could have received treatment which was not recognised as best practice. The complainant was sure that this represented a breach of Clause 2, as inappropriate treatment recommendations were made; Clause 2 stated that activities associated with promotion must never be such as to bring discredit upon or reduce confidence in the pharmaceutical industry.

The complainant noted that the Panel considered that it could not make a judgement on the specific criticisms raised because it had insufficient details of the protocol agreed with the practice. The protocol was in fact the standard one provided in the Protocol Documentation, the only deviation being that on the consent form, the option of the nurse discussing medication issues with the practice pharmacist was also included.

The protocol also specified that compliance assessment was to be included as part of the clinic process. However, while the compliance box was filled in on the patient review forms, it was clear that a full assessment of compliance by collection rate had not been carried out for at least some of the patients.

The quality of this service was such that every recommendation made by the agency nurse needed verification by a GP prior to implementation. The time involved in investigating these recommendations was probably as great as if the patients had been seen by a health professional who was already a member of the practice staff, and therefore the provision of this service was of benefit to neither the practice nor the patients. The complainant thus alleged a breach of Clause 9.1 as she did not believe that the work of the agency nurse was of the highest standard.

As the agency nurse was recommending Seretide inappropriately, this contravened paragraph (vi) of the supplementary information to Clause 18.1, which stated that sponsored health professionals should not be involved in the promotion of specific products.

GlaxoSmithKline could not absolve itself of responsibility for the manner in which the project was conducted by claiming that the review was conducted by an independent company. It had funded the company to carry out the reviews, which in the opinion of the complainant likened the role of this independent company to that of a subcontractor. In other walks of life, the main contractor was ultimately responsible for the work of the subcontractor on any particular project, and the complainant did not see why this situation should be considered to be different.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline stated that whilst it understood the complainant's concerns about the necessary ethical considerations in proposing an industry sponsored patient review, it considered it had taken every step and precaution to ensure high quality and ethical patient review whilst respecting patient confidentiality and the independence of all health professionals involved.

The APRS was a service sponsored by GlaxoSmithKline. It was underpinned by extensive documentation and training that had been used extensively and which had met with the approval of many health professionals.

The challenges for any sponsor in providing this support and ensuring ethical patient review which complied with the Code were as follows:

- To enable a professional, independent nurse of high quality and appropriate training and experience to work in a practice under the close supervision of the GPs, to protocols agreed and determined by the practice;
- The nurse must be employed by an independent third party and must be able to make clinical decisions within the framework set by the practice;
- The nurse must not be given any incentive to make any particular treatment choice and all decisions should be transparent and open to scrutiny;
- The nurse's clinical decisions should be her own as a responsible qualified health professional;
- The sponsor must not have access to any patient identifiable information and must leave clinical supervision to the responsible GP.

GlaxoSmithKline submitted that the procedures and protocols associated with the APRS met the above challenges and provided a strong ethical framework which underpinned the service.

GlaxoSmithKline considered that the complainant's fundamental concern was that of appropriateness of clinical decisions by the APRS nurse, and a number of examples of allegedly poor therapeutic decisions were cited.

GlaxoSmithKline noted that the protocols determined that the responsible GP must establish a framework for treatment recommendations and supervise and approve any treatment changes made. The Therapy Recommendation Form clearly stated that it must be completed by a GP from the practice and the agency nurse in order to ensure that any recommendations made by the agency nurse following patient reviews in clinic were in concordance with the protocols used for treatment within the practice. It appeared from the complainant that practice staff were able to review each case and decide upon the appropriateness of the management of each individual patient as per the terms of the protocol operating in the practice and agreed by them.

GlaxoSmithKline submitted that under the protocol it was clear that the company could not have access to case details to allow it to judge, or be able to influence management choices or therapeutic interventions. As the company was thus prevented from accessing patient details by the protocols in place, it was impossible for it to comment on the individual cases cited by the complainant. GlaxoSmithKline

considered that this was right and proper, and not in any way an abrogation of its responsibility, suffice to state that it had every confidence in the process followed and the individual concerned.

GlaxoSmithKline submitted that these clinical decisions were a matter of professional opinion; the final responsibility had lain with the GP and GlaxoSmithKline did not, and would not wish to, interfere with the nurse's or the GP's views.

GlaxoSmithKline submitted that the agency nurse performing this review was experienced with an impressive CV and independent qualifications in asthma management. Her references were of high quality and testimonials from other practices where the APRS had been performed were flattering. The nurse had received balanced, independent training in asthma and achieved marks of 95% and 100% in her asthma examinations in 2004.

GlaxoSmithKline submitted that the nurse's remuneration was not based on recommendations, sales or prescriptions for specific medicines or groups of medicines; there were no incentives that could be interpreted as biasing her professional judgement.

GlaxoSmithKline submitted that the protocols supporting the review were completed fully in this case; they were clear and explicit about the need for GP approval. Patently in this case the safeguards built in to the protocols worked, since the practice had been able to review each case as proscribed. Indeed it appeared to GlaxoSmithKline that the very review stipulated by the protocol raised an issue as perceived by the complainant.

GlaxoSmithKline strongly disagreed with the assertion that the 'quality of the service' (the implication being that it was poor) required verification of every recommendation. This review was a requirement of the protocol as agreed with the practice.

In summary GlaxoSmithKline noted the following:

- Patient review of chronic diseases was consistent with NHS targets;
- Many patients with respiratory disease were under treated according to NHS targets. Providing additional resource to support the NHS in its reviews had significant patient benefit in improving asthma care;
- About 1,500 patients a year died from asthma;
- GlaxoSmithKline believed that it had constructed a protocol of the highest quality to support patient review in asthma to generate patient benefit while meeting all ethical requirements;
- GlaxoSmithKline believed that its relationship with the agency employing the nurse was appropriate and ethical;
- The nurse in this case had demonstrated, through training, CV, qualifications, testimony and recent examination passes, that she was an appropriately trained nurse of high quality operating to high standards;
- There was no incentive or guidance to encourage any particular therapeutic changes;
- The protocol, and safeguards within it, had worked since the transparency within processes and the necessary approval by a clinician had led to this being perceived as a potential issue;
- It was inappropriate for GlaxoSmithKline to review clinical records. GlaxoSmithKline relied on the agency to train, monitor and appraise nurses in accordance with agreed schedules;
- At the root of this issue was a difference of clinical opinion – a not infrequent event in everyday practice – and one that was dealt with in the normal way between a GP and a nurse regardless of the nurse's employer, be they a district nurse, practice nurse or, in this case, a nurse employed by an agency. In addition, this issue might have arisen in part due to a misunderstanding of the aims and objectives of the APRS by the complainant, and perhaps a degree of mistrust in the intentions or company-sponsored patient review. GlaxoSmithKline believed that this was not borne out by the evidence submitted.

For the reasons stated above GlaxoSmithKline denied a breach of Clause 18.1 since the agreement to the treatment protocols and their implementations, including supervision of the nurse and case review, were entirely in the hands of the practice. The company also denied a breach of Clause 9.1 since for the reasons above it had taken every reasonable step to ensure satisfactory and ethical provision of support for patient review. Finally, GlaxoSmithKline denied a breach of Clause 2 since these protocols and the agency nurses had been inspected by third parties (clinicians and prescribing advisers) and had met with approval.

GlaxoSmithKline submitted that the APRS aimed to provide resource to assist the NHS in the review of asthma patients. The intent, documentation and implementation of the scheme was a source of pride for GlaxoSmithKline through the provision of additional independent resource for direct patient benefit. GlaxoSmithKline considered that such schemes operated in this manner should support the positive reputation of the industry. The complaint in this case appeared to revolve around a difference in clinical opinion, and not as any consequence of perverse activity or incentives.

COMMENTS FROM COMPLAINANT

No further comments were made by the complainant.

APPEAL BOARD RULING

The Appeal Board noted GlaxoSmithKline's submission that it was satisfied the protocol was followed and that the complaint revolved around a difference in clinical opinion. GP signatures were obtained at all stages of the service including therapy recommendations. No therapy recommendations were made in 15 of the 29 patients reviewed. Further, the practice did not implement any of the therapy recommendations suggested. The Appeal Board noted the complainant's submission on this point.

The Appeal Board was concerned about the gravity of the complainant's allegations with respect to the recommendations made by the sponsored nurse at the practice in question and noted that extreme dissatisfaction was normally necessary on the part of a health professional before he/she was moved to submit a complaint. GlaxoSmithKline had submitted that it had no access and hence no knowledge of the individual cases in question. The Appeal Board did not know the details of each patient's case and it considered that without these it was impossible to make a judgement on the specific criticisms raised by the complainant.

The Appeal Board noted the complainant's comments about the recommendations made by the sponsored nurse in relation to COPD patients. The Appeal Board noted that it did not have the protocol agreed in the practice before it. The complainant stated that the protocol agreed with the practice was the standard protocol as in the documentation with one change to include the option of the nurse discussing medication issues with the practice pharmacist. Notwithstanding the wisdom of any of the recommendations made by the sponsored nurse with respect to specific patients, the Appeal Board noted that none of them had been implemented and that the GPs in the practice had made the final decisions about individual patient management. The protocol was thus robust in that regard.

The Appeal Board noted the Panel's previous ruling in Case AUTH/1597/6/04 that overall the APRS was not in breach of Clauses 2, 9.1, 15.2 and 18.1 of the Code.

On the limited evidence before it the Appeal Board considered that it had no option other than to uphold the Panel's rulings that the APRS as implemented in the practice in question was not in breach of Clauses 18.1 or 9.1 of the Code. The appeal on this point was unsuccessful.

The Appeal Board considered that the implementation of APRS in the practice in question did not warrant a ruling of a breach of Clause 2 which was reserved to indicate particular censure. The Appeal Board upheld the Panel's ruling of no breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **20 August 2004**

Case completed **24 February 2005**

HEAD OF MEDICINES MANAGEMENT/DIRECTOR v WYETH

Alleged breach of undertaking

The head of medicines management at a primary care trust (PCT) noted a previous case, Case AUTH/1561/3/04, wherein representatives from Wyeth were ruled in breach of the Code in relation to a switch programme which involved switching patients on Zoton (lansoprazole) capsules to Zoton FasTab. The complainant alleged that company representatives were continuing this activity and seemed unaware of the previous ruling. As the complaint concerned a breach of undertaking it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

Wyeth submitted that the service to which this complaint related was part of a new service which the company had developed further to the outcome of Case AUTH/1561/3/04.

The Panel noted that the complainant had alleged a breach of the undertaking given by Wyeth in Case AUTH/1561/3/04 which concerned a switch programme whereby patients on Zoton capsules were switched to Zoton FasTab; breaches of the Code were ruled.

The Panel considered that its ruling in a previous case, Case AUTH/1606/7/04, was relevant; Case AUTH/1606/7/04 concerned whether the arrangements for Wyeth's revised switch programme were in breach of the undertaking given in Case AUTH/1561/3/04.

In Case AUTH/1606/7/04 the Panel had noted that there were differences between the switch programme at issue in Case AUTH/1561/3/04 and that at issue in Case AUTH/1606/7/04; the revised service was not restricted to a switch from Zoton capsules to Zoton FasTab but was available for any oral proton pump inhibitor (PPI) of the doctor's choice. The Panel noted Wyeth's submission that the prescribing decision of the GP had to be made in writing in advance of the offer of the service. The medication review booklet explained that the Gastrocare service was available to review any oral PPI dose at the request of the practice. The representatives' 'Action plan: Gastrocare service offerings' explained that if the GP chose to change from one formulation of a PPI medication to another in a dose for dose switch, the most suitable service was the GP System Specialist Implementation. If any other change was required, or if the GP did not wish for this service, the GP was offered the Gastrocare Audit Review.

The Panel had considered that the service at issue in Case AUTH/1606/7/04, was sufficiently different from that considered in Case AUTH/1561/3/04; the service was no longer restricted to switches from Zoton capsules to Zoton FasTab but was available for all oral PPIs. The Panel considered there was no breach of the undertaking previously given. The Panel had therefore ruled no breach of the Code.

Turning to the present case, Case AUTH/1629/9/04, the Panel noted that it appeared that the activity at issue in the present complaint concerned the revised service, the subject of Case AUTH/1606/7/04. Further Wyeth had submitted that the materials and service at issue in the present case concerned the revised service and were the same as those considered in Case AUTH/1606/7/04.

Whilst the complainant had mentioned the representatives' level of awareness about the Panel ruling in Case AUTH/1561/3/04, the Panel did not consider that the complaint required it to consider whether the role of the representative in relation to the revised service was acceptable. The Panel nonetheless noted that this was the subject of a separate complaint, Case AUTH/1652/11/04.

In the present case, the Panel considered that the rulings in Case AUTH/1606/7/04 applied. No breach of the Code was ruled, including no breach of Clause 2.

The head of medicines management at a primary care trust (PCT) complained about the activities of representatives from Wyeth Pharmaceuticals. The complainant referred to an article in the BMJ 26 June which discussed Case AUTH/1561/3/04 wherein Wyeth had been ruled in breach of the Code in relation to a switch programme.

Upon receipt of the complaint the Director decided that as two similar complaints were being considered (Cases AUTH/1606/7/04 and AUTH/1617/6/04) consideration of this case should wait until the conclusion of Case AUTH/1606/7/04.

As the case involved an alleged breach of undertaking, that aspect of the complaint was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings. This accorded with advice previously given by the Code of Practice Appeal Board.

COMPLAINT

The complainant referred to the article in the BMJ, 26 June, and noted that Wyeth representatives were still signing practices up to switch all patients on Zoton (lansoprazole) capsules to Zoton FasTab. The representatives seemed unaware of the previous ruling.

When writing to Wyeth the Authority asked it to respond in relation to Clauses 2, 9.1 and 22.

RESPONSE

Wyeth noted that the present complaint was similar to Case AUTH/1606/7/04 for which no breach was ruled. [Case AUTH/1606/7/04 concerned whether the revised switch programme was in breach of the undertaking given in Case AUTH/1561/3/04].

Wyeth submitted that it had fully complied with the undertaking given in Case AUTH/1561/3/04. The Formulary Based Implementation (FBI) service and all associated materials in respect of which the undertaking was given were withdrawn with

immediate effect from the sales force by a memorandum and the FBI service had not been offered nor materials used since June 2004. Wyeth provided a copy of a memorandum (reference WZZOT/2004/0018) and associated forms, all of which were completed in accordance with the procedure stated therein. The service offering to which this query now related was part of the new service offering (described below) which Wyeth subsequently designed and developed in order to avoid any further breaches of the Code following the outcome of Case AUTH/1561/3/04. Wyeth considered that this service offering and associated material was fully Code compliant and confirmed that the activity carried out by Wyeth representatives at the time of this complaint was in accordance with Code-compliant company procedures.

Wyeth's service range offering relating to the gastrointestinal (GI) therapy area had been redesigned and developed, and the new range launched, so that all such services offered were non-brand specific and therefore could be offered and performed in respect of any relevant brand of medicine (ie proprietary or generic) of the GP's choice. Further, the new material and the material use sequence now made it clear that the GP's prescribing decision had been made in advance of any offer of a service to assist in implementing that decision being made by Wyeth. The service offering now clearly fell under the provisions of Clause 18.1 of the Code and the supplementary information for that clause which allowed the provision of medical and educational services which would enhance patient care or benefit the NHS if they were provided in such a way as to not be an inducement to prescribe any medicine.

The company's designated procedure was as follows:

1 The GP expressed an interest in a review of their or their practice's proton pump inhibitor (PPI) prescribing.

2 In a visit separate to any product-related visit, or in a clearly separated part of the same visit, and following confirmation from the GP that they had an interest in a review of their or their practice's PPI prescribing, the representative followed the procedure as set out in the representative briefing document 'Action Plan: GastroCare Service Offerings' (ZZOT3580), the relevant pages of which were provided. Briefly, the GP completed and signed the Medication Review Spreadsheet to illustrate the prescribing decision s/he had made or was making and wanted to implement. If the only medication change the GP wished to make, as shown by the completed Medication Review Spreadsheet, was that of changing prescribing from one formulation of the same PPI to another in a dose for dose switch, then in order to assist the GP in implementing that prescribing decision the representative offered the service most appropriate to that type of change, in this case the GP Systems Specialist Implementation (GPSSI) service, using the GPSSI Pack (ZZOT3588) to show the GP how the service would be carried out. If the GP decided to accept the service offering, the Practice Booking and Consent Form was completed by the GP and arrangements then made by the Wyeth representative with an external supplier to carry out the service.

In respect of the allegation that the 'representatives seemed unaware of the previous ruling', Wyeth stated that the regional business managers (RBMs) were given a presentation as part of a workshop at their quarterly management meeting held on 9 June 2004. The presentation included a section on the outcome of the Zoton FasTab promotion complaint and a description of the new revised service offering, plus a clear reminder regarding the product and service separation aspect. The relevant part of this presentation was enclosed (ZZOT3589). The RBMs were also provided with a GastroCare Process Flowchart, the section relevant to the service in question was provided (ZZOT3601). The RBMs then cascaded the information presented to them and provided the Flowcharts to the sales representatives as part of their own regional meetings. The sales representatives were also provided with the Action Plan (ZZOT3580). The field force was advised that all services signed up under the withdrawn FBI Service documentation must be re-signed using the new GPSSI Service documentation and procedure. As the withdrawn FBI Service would take only a few hours, or at the most one day to complete depending on patient list size, the situation where a service had been started but not completed would not arise.

The RBM presentation referred to product and service separation and the Flowchart began with an instruction for the sales representative to close the product call before commencing any discussion relating to service. Although the importance of product and service separation was known and understood by the field force, these points were verbally reinforced by the RBMs when cascading this information to the representatives.

Wyeth therefore considered that there had been no activity or materials associated with promotion which had brought discredit upon, or reduced confidence in, the pharmaceutical industry and therefore no breach of Clause 2 of the Code. High standards were maintained at all times both by the conduct of Wyeth representatives and by the content and use of all material associated with the relevant service offering and therefore there had been no breach of Clause 9.1. Wyeth had ensured that it had complied with all aspects of the undertaking given in respect of Case AUTH/1561/3/04 and hence there had been no breach of Clause 22 of the Code.

PANEL RULING

The Panel noted that the complainant had alleged a breach of the undertaking given by Wyeth in Case AUTH/1561/3/04. Case AUTH/1561/3/04 concerned a switch programme whereby patients on Zoton capsules were switched to Zoton FasTab; breaches of Clauses 9.1 and 18.1 of the Code were ruled.

The Panel considered that its ruling in a previous case referred to by Wyeth, Case AUTH/1606/7/04, was relevant; Case AUTH/1606/7/04 considered whether the arrangements for Wyeth's revised switch programme were in breach of the undertaking given in Case AUTH/1561/3/04.

Panel ruling in Case AUTH/1606/7/04

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 the industry that companies complied with undertakings.

The Panel noted that the previous case, Case AUTH/1561/3/04, concerned the FBI service whereby patients on Zoton capsules were switched to Zoton FasTab. The Panel had considered that the FBI Service was part of the promotion of Zoton FasTab; it was not described as anything else in the material. The service could thus not benefit from the supplementary information to Clause 18.1 regarding the provision of medical and educational goods and services. The Panel noted Wyeth's submission that Zoton FasTab was 10% less expensive than Zoton capsules. Switching patients from Zoton capsules to Zoton FasTab was thus a less expensive way of prescribing Zoton. Companies could of course promote products on the basis of cost and it was not unreasonable to note savings that a practice might make by switching from one product to another. The difficulty was when the company paid directly or indirectly for those changes to be made because then the company's actions amounted to it paying to boost the prescription of a specific medicine. In this regard, the Panel noted that the switch programme at issue involved two products marketed by the same company; prescriptions for Zoton FasTab were not being generated at the expense of another company's product. Nonetheless, Clause 18.1 of the Code stated that 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend or buy any medicine, subject to the provisions of Clause 18.2'. Thus in the Panel's view it was immaterial that the two medicines at issue were marketed by the same company. The provision of the FBI Service by Wyeth would benefit a practice by saving it the expense of carrying out the switch itself. The arrangements amounted to a pecuniary advantage given as an inducement to prescribe Zoton FasTab. Breaches of Clauses 9.1 and 18.1 had been ruled.

The Panel noted that there were differences between the switch programme at issue in Case AUTH/1561/3/04 and the service at issue in the present case, Case AUTH/1606/7/04; the present service was not restricted to a switch from Zoton capsules to Zoton FasTab but was available for any oral PPI of the doctor's choice. The Panel noted Wyeth's submission that the prescribing decision of the GP had to be made in writing in advance of the offer of the service. The medication review booklet (ref ZZOT3587) explained that the Gastrocare service was available to review any oral PPI dose at the request of the practice. The representatives' 'Action plan: Gastrocare service offerings' explained that if the GP chose to change from one formulation of a PPI medication to another in a dose for dose switch, the most suitable service was the GP System Specialist Implementation. If any other change was required, or if the GP did not wish for this service, the GP was offered the Gastrocare Audit Review.

The Panel noted that representatives were instructed that all practices signed up under the withdrawn FBI service must be re-signed under the new service. The regional business managers had been told why the previous service was withdrawn and instructed the representatives in relation to the revised service. Representatives had to confirm that documentation in relation to the original service was returned to head office or destroyed locally.

The Panel noted Wyeth's submission that the complainant had requested a review of his PPI prescribing from Zoton to Zoton FasTab and had informed the representative at the outset that this prescribing decision had been agreed with the relevant PCT. The Panel also noted Wyeth's submission that the medication review spreadsheet was completed and signed before any service offerings were discussed.

The booklet GP Systems Specialist Implementation Pack (ref ZZOT3585) explained the role of the GP Systems Specialist in relation to the implementation of the GP prescribing requests as set out in the medication review spreadsheet. Wyeth submitted that this was the procedure to be implemented in the complainant's practice. No details were provided about the alternative service, the Gastrocare audit review. The Panel noted, however, that it was not the subject of complaint.

The Panel considered the arrangements only in relation to the alleged breach of undertaking. It did not consider the arrangements in relation to the requirements of Clause 18.1 as it had no complaint in that regard. The Panel considered that the service at issue was sufficiently different from that considered in Case AUTH/1561/3/04; the service was no longer restricted to switches from Zoton capsules to Zoton FasTab but was available for all oral PPIs. The Panel considered there was no breach of the undertaking previously given. The Panel had therefore ruled no breach of Clause 22. It thus followed there had been no breach of Clauses 9.1 or 2.

Case AUTH/1629/9/04

The Panel noted that the complainant had stated that the representatives seemed unaware of the ruling discussed in the BMJ article: Case AUTH/1561/3/04. The position was complicated. The complainant had referred to the activity outlined in the BMJ article of 26 June 2004. The present complaint, however, was dated 7 September. Wyeth had submitted that the FBI service and all associated materials at issue in Case AUTH/1561/3/04 were withdrawn by a memorandum with immediate effect from 7 June. It thus appeared that the activity at issue in the present complaint concerned the revised service; the subject of Case AUTH/1606/7/04. Further Wyeth had submitted that the materials and service at issue in the present case concerned the revised service and were the same as those considered in Case AUTH/1606/7/04.

Whilst the complainant had mentioned the representatives' level of awareness about the Panel ruling in Case AUTH/1561/3/04, the Panel did not consider that the complaint required it to consider

whether the role of the representative in relation to the revised service was acceptable in relation to the requirements of Clause 18.1. The Panel nonetheless noted that this was the subject of a separate complaint, Case AUTH/1652/11/04.

Turning to the present case the Panel considered that the rulings in Case AUTH/1606/7/04 applied here. No breach of Clauses 22, 9.1 and 2 was ruled.

Case commenced **7 September 2004**

Case completed **11 February 2005**

CASE AUTH/1634/9/04

BRISTOL-MYERS SQUIBB and OTSUKA v LILLY

Promotion of Zyprexa

Bristol-Myers Squibb and Otsuka complained jointly about the promotion of Zyprexa (olanzapine) by Lilly. Bristol-Myers Squibb and Otsuka supplied Abilify (aripiprazole). Both Zyprexa and Abilify were indicated for the treatment of schizophrenia.

In a mailer sent to psychiatrists and hospital psychiatric pharmacists a table of data listed those antipsychotics, including Zyprexa, which were significantly better than haloperidol and those, including aripiprazole, which were equivalent to haloperidol. The complainants alleged that the table did not reflect the conclusions of the meta-analysis by Davis *et al* (2003) upon which it was based. Davis *et al* clearly stated in its efficacy section 'Failure to find a statistically significant difference does not prove that these drugs are equal to [first generation antipsychotics] because there is a possibility that further studies could demonstrate this'. 'These drugs' included aripiprazole, and haloperidol was a first generation antipsychotic. Furthermore, since the publication of Davis *et al* new data demonstrated that aripiprazole had comparable or superior long-term efficacy to haloperidol (Kasper *et al* 2003).

The Panel noted that Davis *et al* had reviewed 142 controlled studies of second generation antipsychotics; only 3 had involved aripiprazole. The Panel considered that the table of data implied that Davis *et al* had unequivocally demonstrated that aripiprazole and haloperidol were equivalent in terms of efficacy. This was not so. The Panel further noted that later data (Kasper *et al*) had shown that aripiprazole was at least as effective as haloperidol. The Panel considered that the table of data was misleading. Breaches of the Code were ruled which were appealed by Lilly. The Panel did not consider that aripiprazole had been disparaged. No breach of the Code was ruled in that regard.

Upon appeal by Lilly the Appeal Board noted that Davis *et al* contained limited data on Abilify; the patient population for aripiprazole included in the meta-analysis was 560 out of a total patient population of 21,020. The Appeal Board noted the author's comments regarding the significance of not finding a statistically significant difference between products. The Appeal Board considered that the table of data was too simplistic; it implied that Davis *et al* had unequivocally demonstrated that aripiprazole and haloperidol were equally effective. This was not so. The Panel's rulings were upheld.

Immediately below the table of data considered above was the bullet point 'The results of this meta-analysis are consistent with those observed in SOHO, the largest naturalistic study conducted to date (>10,000 patients)'. This bullet point was immediately followed by a bar chart showing the proportion of patients responding to monotherapy (Zyprexa, risperidone, quetiapine or oral typical).

Bristol-Myers Squibb and Otsuka alleged that the bar chart and bullet point were misleading and that consistency between SOHO and Davis *et al* could not be inferred. The companies noted in particular that Davis *et al* included aripiprazole but SOHO did not and that efficacy measures were not consistent; the data displayed from SOHO was positive (CGI) symptoms whereas Davis *et al* used a variety of efficacy measures.

The Panel noted that aripiprazole was not included in the SOHO study and so in that regard the findings of SOHO and Davis *et al* could not be consistent. The Panel considered that the claim was thus inaccurate. A breach of the Code was ruled which was upheld on appeal by Lilly. The Panel did not consider that the claim disparaged aripiprazole as alleged. No breach of the Code was ruled.

Bristol-Myers Squibb and Otsuka alleged that a table of data in a Zyprexa discussion aid was unbalanced and disparaged aripiprazole. The table reviewed features of antipsychotics, including Zyprexa and aripiprazole, which appeared to have been selected such that Zyprexa had an entirely positive profile. Features beneficial to other antipsychotics (eg weight neutrality, lack of sedation) were not mentioned. Further confusion was added by the fact that the Zyprexa data referred to both the oral and the rapid acting intramuscular (IM) formulation although this was not clear. Some readers might assume that 'begins to reduce positive symptoms within two hours' related to oral Zyprexa when in fact this was a property of the IM formulation.

The Panel noted that the discussion aid was entitled 'Considering the options in acute schizophrenia'. The inside pages referred to the start of therapy and the management of schizophrenia from day 1. The Panel considered that it was clear that the discussion aid was about the initial treatment of schizophrenia and not its long-term management. In that regard the list of criteria was not inappropriate – weight

neutrality was not an issue in the initial treatment of schizophrenia and sedation as a side-effect could be useful in the initial stages of an acute attack. The Panel did not consider that the discussion aid was misleading in that regard and ruled no breach of the Code. The Panel did not consider that aripiprazole had been disparaged. No breach of the Code was ruled.

The Panel noted that the discussion aid promoted Zyprexa the brand and not a particular formulation of the medicine. Two features listed ie 'Indicated for rapid control of agitation and disturbed behaviours' and 'Reduces agitation within 15 minutes' were followed by an asterisk which referred to the footnote 'Rapid-acting IM formulation'. The Panel considered that, as presented, the claims were unqualified, the footnote had to be read in order to fully understand the context in which the claims were made. The Panel thus considered that the table of data was misleading. Breaches of the Code were ruled. The Panel did not consider that aripiprazole had been disparaged. No breach of the Code was ruled.

Bristol-Myers Squibb Pharmaceuticals Limited and Otsuka Pharmaceuticals (UK) Ltd complained jointly about two promotional items for Zyprexa (olanzapine) issued by Eli Lilly and Company Limited. The items at issue were a mailer sent to psychiatrists and hospital psychiatric pharmacists (ref ZY2394) and a discussion aid (ref ZY2350). Correspondence between the parties had allayed some concerns but not others.

Bristol-Myers Squibb and Otsuka supplied Abilify (aripiprazole). Both Zyprexa and Abilify were indicated for the treatment of schizophrenia.

A Mailer ZY 2394

1 Table of data depicting the results of Davis *et al* (2003)

A table of data, divided into two columns listed those antipsychotics which were significantly better than haloperidol (Zyprexa, risperidone, amisulpride and clozapine) and those antipsychotics which were equivalent to haloperidol (quetiapine, aripiprazole, sertindole and zotepine).

COMPLAINT

Bristol-Myers Squibb and Otsuka complained that the table of data did not reflect the conclusion of the meta-analysis by Davis *et al* upon which it was based. Aripiprazole was shown to be equivalent to haloperidol which was inaccurate and disparaging. Davis *et al* clearly stated in its efficacy section 'Failure to find a statistically significant difference does not prove that these drugs are equal to [first generation antipsychotics] because there is a possibility that further studies could demonstrate this'. The reference to 'these drugs' included aripiprazole, and haloperidol was a first generation antipsychotic.

Furthermore, Davis *et al* no longer constituted an up-to-date evaluation of all the evidence; new clinical trial data did not support equivalence of aripiprazole to haloperidol, indeed since the publication of Davis *et al* there had been six more papers published. One of these studies compared the efficacy and safety of aripiprazole with haloperidol for long-term maintenance treatment following acute relapse of schizophrenia (Kasper *et al*, 2003). That paper concluded that:

- aripiprazole demonstrated comparable or superior long-term efficacy to haloperidol across all symptom measures including significantly greater improvements for PANSS negative subscale scores and MADRS total score
- the time to discontinuation for any reason was significantly greater with aripiprazole than with haloperidol
- time to discontinuation due to adverse events or lack of efficacy was significantly greater with aripiprazole than haloperidol
- when a more stringent response criterion was used [30% improvement in PANSS total score maintained for at least 28 days and one additional visit] aripiprazole produced a significantly higher response rate than haloperidol.

These data supported the fact that it was inappropriate for aripiprazole to be described as equivalent to haloperidol.

Bristol-Myers Squibb and Otsuka considered that the table was inaccurate. It was not based on an up-to-date evaluation of all the evidence and did not conform to the letter and spirit of the Code. It also disparaged aripiprazole. The companies alleged breaches of Clauses 7.2, 7.8 and 8.1 of the Code.

RESPONSE

Lilly submitted that the table showed the findings from Davis *et al* that one group of four antipsychotics were significantly better than haloperidol whereas the other group of four antipsychotics were equivalent. Lilly did not consider that this was a misleading interpretation of the conclusion of this meta-analysis, which stated in the abstract of the paper 'Conclusion: Some [second generation antipsychotics] are more efficacious than [first generation antipsychotics], and, therefore, [second generation antipsychotics] are not a homogenous group'. With respect to the allegation that this was not a balanced representation of the data, the table presented the results for antipsychotic drugs available in the UK as described by the authors, who stated 'Results: Using the Hedges-Olkin algorithm, the effect sizes of clozapine, amisulpride, risperidone and olanzapine were 0.49, 0.29, 0.25 and 0.21 greater than those of [first generation antipsychotics], with P values of $2x10^{-8}$, $3x10^{-7}$, $2x10^{-12}$, and $3x10^{-9}$, respectively. The remaining 6 [second generation antipsychotics] were not significantly different from [first generation antipsychotics], although zotepine was marginally different'. The mailer simply listed the medicines available in the UK and grouped them in the categories described by Davis *et al*.

Lilly noted that Bristol-Myers Squibb and Otsuka had stated that the above might not be correct as further

studies could demonstrate a different conclusion. Indeed the possibility of further studies refuting any existing beliefs of clinicians relating to comparative efficacy and safety could not be excluded. The meta-analysis was an up-to-date analysis of the various atypical antipsychotics and there was no evidence that it had been superseded. Davis *et al* stated that they planned to regularly update their meta-analysis on the Internet and gave the website address. Lilly had accessed this website on 22 September 2004 and the conclusions of the meta-analysis had not changed. On the same day a Medline search using the criteria 'efficacy AND antipsychotic AND schizophrenia AND meta-analysis' found 36 results. Of the publications identified only two peer reviewed meta-analyses were published after the Davis *et al* meta-analysis and made comparisons of atypical antipsychotics versus typical antipsychotics or placebo (Schulz *et al* 2003 and Sprague *et al* 2004). The two publications did not contradict the findings of Davis *et al*. They concluded that direct comparisons between other atypical antipsychotics were not available. Systematic reviews (indirect comparisons) of placebo-controlled or traditional antipsychotic-controlled trials suggested similar efficacy for quetiapine, olanzapine, and risperidone when placebo was the comparator and inferior efficacy of quetiapine compared to olanzapine and risperidone when haloperidol was the comparator.

Lilly noted that Bristol-Myers Squibb and Otsuka had referred to six papers published since Davis *et al* but had only specifically referred to Kasper *et al* 2003. Unfortunately the complainants did not clarify that these six publications did not mean six new clinical studies. Lilly knew of only four aripiprazole clinical trials published in peer reviewed journals. Kasper *et al* was received by the journal in October 2002, accepted in July 2003 and then published later that year. The three other clinical trials published were Kane *et al* (2002), Potkin *et al* (2003) and Pigott *et al* (2003). Only Kane *et al* and Potkin *et al* compared aripiprazole with haloperidol and in each the efficacy of aripiprazole was shown to be equivalent to haloperidol. In Case AUTH/1623/8/04 it was ruled that aripiprazole was not superior to haloperidol over 52 weeks using data derived from Kasper *et al*. Furthermore this study data (presented under the authorship of Kujawa *et al*) had been shown at numerous meetings around the world over the last few years as posters and abstracts. What was clear was that using the primary study endpoints as defined by Kujawa *et al*, aripiprazole was not superior to haloperidol either in response rates or in 'time to failure to maintain response'. The poster from Kujawa *et al* clearly stated these findings. The study conclusions summarised by the complainants did not appear to make this clear. Lilly did not consider that the findings and conclusions from Davis *et al* were anything other than up-to-date and thus could reasonably be used and that the table accurately summarised the results of the meta-analysis.

Lilly stated that the recent Cochrane review (Aripiprazole for Schizophrenia 2004) did not supersede Davis *et al* but gave some helpful knowledge regarding the complete aripiprazole clinical trial base. This independent group reviewed all clinical randomised trials comparing aripiprazole with placebo, typical or atypical antipsychotic drugs. They stated their clear concerns regarding the quality of the data that was available to them. In particular they stated 'enormous efforts were invested in studies rating and recording data that are then reported in such a way as to render them useless for reviews such as this'. The Cochrane group also rated all trials as category B ('moderate risk of bias – some doubt about the results'). The general conclusions were that much of the aripiprazole clinical trial data could not be used because of poor reporting and they expressed concerns that trial participants might be 'appalled' to realise how little of the data could be used. Their evaluation of aripiprazole versus typicals nevertheless was that 'there were no significant benefits for aripiprazole with regards to global state, mental state, quality of life or leaving the study early'. The failure to provide standard deviations was specifically noted. The Cochrane group furthermore felt unable to use data that was specifically listed by the complainants (and included in the Kasper paper) including PANSS and MADRS measurements.

Lilly noted that the consensus on hierarchy of evidence which rated robustly performed meta-analyses as the highest level of evidence, with single randomised controlled trials occupying the second tier (BAP Bipolar Guidelines 2003).

Lilly submitted that the current literature to the best of its knowledge reflected the conclusions from Davis *et al* in particular that aripiprazole had not been demonstrated to be superior to haloperidol with regard to efficacy.

PANEL RULING

The Panel noted that the table in question was based upon Davis *et al*, a meta-analysis of the efficacy of second-generation antipsychotics. The meta-analysis reviewed 142 controlled studies. The Panel noted, however, that not all of the medicines were equally represented. For example 31 studies involving clozapine were included in the meta-analysis vs three for aripiprazole (n=560); (Carson *et al* 2001; Daniel *et al* 2000 and Petrie *et al* 1997). The data was thus more compelling that there was an advantage for clozapine vs haloperidol as opposed to the equivalence of haloperidol and aripiprazole. Davis *et al* stated that 'Failure to find a statistically significant difference does not prove that these drugs are equal to [first generation antipsychotics] because there is a possibility that further studies could demonstrate this'.

The Panel noted that Kasper *et al* had been published after Davis *et al*. The study investigated the long-term safety and efficacy of aripiprazole (30mg/day) relative to haloperidol (10mg/day) in two 52-week, randomized, double-blind, multicentre studies in 1294 patients in acute relapse with a diagnosis of chronic schizophrenia and who had previously responded to antipsychotics. The authors concluded that aripiprazole demonstrated efficacy equivalent or superior to haloperidol with associated benefits for safety and tolerability.

The Panel considered that the table of data at issue implied that Davis *et al* had, unequivocally

demonstrated that aripiprazole and haloperidol were equivalent in terms of efficacy. This was not so. The Panel further noted that later data (Kasper *et al*) had shown that aripiprazole was at least as effective as haloperidol. The Panel considered that the table of data was misleading. Breaches of Clauses 7.2 and 7.8 were ruled which were appealed by Lilly. The Panel did not consider that the table of data disparaged aripiprazole. No breach of Clause 8.1 was ruled.

APPEAL BY LILLY

Lilly noted that Davis *et al* had concluded 'Some [second-generation antipsychotics] (clozapine, amisulpiride, risperidone and olanzapine) are significantly more efficacious than [first-generation antipsychotics], whereas others are not proven to be so.' The table bore the title 'A large-scale, independent meta-analysis of 124 randomised controlled trials has shown that not all atypicals are equally effective'.

Davis *et al* found that clozapine, amisulpiride, risperidone and olanzapine had effect sizes that were statistically significantly greater than those for first generation antipsychotics. The remaining six second-generation antipsychotics were not significantly different from first-generation antipsychotics. The table was divided into two columns, those medicines stated by Davis *et al* to have significantly greater effect sizes than first-generation antipsychotics were listed under the heading 'significantly better than haloperidol' and those not found to be significantly different to first-generation antipsychotics were listed under the heading 'Equivalent to haloperidol'. The table only listed those medicines licensed in the UK.

Lilly noted that the Panel had noted that Davis *et al* stated 'Failure to find a statistically significant difference does not prove that these drugs are equal to [first-generation antipsychotics] because there is a possibility that future studies could demonstrate this.' This was in the results section of the paper where efficacy differences were discussed. Lilly submitted that the sentence was quoted out of context. It was taken from a paragraph in which Davis *et al* rejected the assertion made by Geddes *et al* (2000) that second-generation antipsychotics were equally efficacious as a homogenous group because of the large amount of variance attributable to the different medicines. Davis *et al* then listed the second-generation antipsychotics that showed similar efficacy to first-generation antipsychotics in the sense that improvement scores produced by these medicines were not significantly better than those of first-generation antipsychotics. Davis *et al* acknowledged that future studies could change this result. This was true of all studies where no difference was seen. Nevertheless, using the available data up until May 2002, there were statistically significant differences between the second-generation antipsychotics analysed. Lilly was not aware of any data published since then that would materially change this result.

Lilly noted that the complainants had stated that Davis *et al* was no longer up to date as there had subsequently been six more aripiprazole papers published. As far as Lilly was aware the only new data comparing aripiprazole versus an active comparator was Kasper *et al* (2003). When the results of this study were recently considered by the Panel (Case AUTH1623/8/04), it was concluded that superiority of aripiprazole versus haloperidol for the primary endpoint at three time points out of twenty did not justify a claim of superiority of aripiprazole. Inclusion in the Davis *et al* meta-analysis of this additional study in which the effect size of aripiprazole was no greater than that for haloperidol would be very unlikely to change the result beyond making the 95% confidence interval for the aripiprazole data smaller. Lilly was not aware of any subsequent meta-analyses that reached an alternative conclusion and superseded Davis *et al*. Lilly noted that the recent Cochrane Review (Aripiprazole for Schizophrenia 2004) stated in its evaluation of aripiprazole versus typicals that 'there were no significant benefits for aripiprazole with regards to global state, mental state, quality of life or leaving the study early'.

Lilly noted the Panel's note that not all of the medicines were equally represented in the Davis *et al* meta-analysis and stated that the data would thus be more compelling for those medicines that had a greater research base. Lilly alleged that this was not an entirely accurate interpretation. Meta-analysis was performed to produce a synthesis of previous studies to obtain a single summary estimate of the results from all available studies. In the hierarchy of evidence, meta-analysis of randomised controlled trials was graded 1a, the highest of 6 grades (J Psychopharmacol 2003). The combination of results from an increasing number of trials would give a more precise summary estimate of the results, which was reflected in a narrower 95% confidence interval. This was because the 95% confidence interval was the range of values within which it was 95% certain that the true mean of the population was found. As the results of more studies became available it was likely that the results obtained would cluster around the true mean for the population sampled. The complainants considered that if Kasper *et al* had been included in Davis *et al* it would have changed the conclusion of the paper. The primary end point in Kasper *et al* for aripiprazole was not significantly different to haloperidol for 17 out of 20 time points. Inclusion of this data in the meta-analysis would be highly likely to produce a more robust estimate of no difference between aripiprazole and haloperidol.

Lilly noted that the Panel had considered that the table of data implied that Davis *et al* had unequivocally demonstrated that aripiprazole and haloperidol were equivalent in terms of efficacy. In Lilly's view, the recipients of the mailing would understand the underlying statistical principles. In summary, claiming statistical significance implied that there was a less than 1 in 20 chance that the difference seen occurred by chance. If statistical significance was not found it was likely that there was no difference between treatment options.

In conclusion, Lilly submitted that the table in question accurately reflected the results and conclusion of Davis *et al* and that the subsequent Kasper *et al* study would not have changed the

conclusions of Davis *et al* because it also demonstrated that aripiprazole had a similar effect size to haloperidol. The meta-analysis itself had not been superseded by any comparable publication. Lilly therefore denied a breach of Clauses 7.2 or 7.8.

COMMENTS FROM BRISTOL-MYERS SQUIBB AND OTSUKA

Bristol-Myers Squibb and Otsuka submitted a joint response to the appeal. The companies alleged that that the information provided in the Lilly mailer did not reflect the conclusion of Davis *et al*. The companies agreed with the Panel ruling that Lilly was in breach of Clauses 7.2 and 7.8 as: not all medicines in Davis *et al* were equally represented; Davis *et al* made the statement that future studies might demonstrate differences between the medicines; Kasper *et al* showed that aripiprazole demonstrated efficacy equivalent or superior to haloperidol; the table in the mailer implied that Davis *et al* had unequivocally demonstrated that aripiprazole and haloperidol were equivalent in terms of efficacy and this was considered misleading by the Panel.

The companies disagreed with Lilly's submission that the statement by Davis *et al* 'Failure to find a statistically significant difference did not prove that these drugs were equal to [first- generation antipsychotics] because there was a possibility that future studies could demonstrate this' had been taken out of context. Although the statement appeared in the results section of the paper, it nonetheless represented the views of the authors, and as such remained valid and relevant.

The companies agreed that Davis *et al* was the most up-to-date meta-analysis at the time; they did not question the validity of the Davis *et al* analysis *per se*, nor did they disparage meta-analysis as a tool for data analysis. Additionally, the companies stated that it was irrelevant to speculate as to the impact of including Kasper *et al* in the Davis *et al* analysis. The complaint was about the fact that the mailer implied that Davis *et al* had unequivocally demonstrated that aripiprazole and haloperidol were equivalent in terms of efficacy; this continued to be misleading, and the points raised by Lilly had not changed this.

Additionally, the companies re-iterated the point that at the time that the mailer was prepared, Kasper *et al*, which showed that aripiprazole demonstrated efficacy equivalent or superior to haloperidol, was published.

In conclusion, the companies agreed with the Panel ruling.

APPEAL BOARD RULING

The Appeal Board noted that the table in question was based upon Davis *et al*, a meta-analysis of the efficacy of second-generation antipsychotics. The Appeal Board noted, however, that not all of the medicines were equally represented. There was limited data on Abilify. For example the patient population for aripiprazole included in the meta-analysis was 560 out of a total patient population of 21,020. Davis *et al* stated that 'Failure to find a statistically significant difference does not prove that [second-generation antipsychotics] are equal to [first-generation antipsychotics] because there is a possibility that further studies could demonstrate this'.

The Appeal Board considered that the table of data at issue was too simplistic; it implied that Davis *et al* had unequivocally demonstrated that aripiprazole and haloperidol were equivalent in terms of effectiveness. This was not so. The Appeal Board considered that the table of data was misleading. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.8 of the Code. The appeal on this point was unsuccessful.

2 Claim 'The results of this meta-analysis are consistent with those observed in SOHO, the largest naturalistic study conducted to date (> 10,000 patients)'

This bullet point was immediately below the table of data at issue in point 1 above and was immediately followed by a bar chart showing the proportion of monotherapy (Zyprexa, risperidone, quetiapine or oral typical) completers responding after 12 months in terms of positive (CGI) symptoms.

COMPLAINT

Bristol-Myers Squibb and Otsuka alleged that the bar chart and bullet point were misleading. To claim that 'The results of this meta-analysis [Davis *et al*] are consistent with those observed in SOHO, the largest naturalistic study conducted to date (> 10,000 patients)' was inaccurate. Aripiprazole was not included in the SOHO study, and no aripiprazole results were displayed on the bar chart. Consistencies between two data sets could not be inferred, when the antipsychotics included, and the measures used in each data set were not comparable – the data displayed from the SOHO study was CGI symptoms; Davis *et al* examined a variety of measures of clinical efficacy. The companies alleged that the bullet point was inaccurate and disparaged aripiprazole in breach of Clauses 7.2 and 8.1 of the Code.

RESPONSE

Lilly considered that Davis *et al* and the SOHO data sets were consistent in that they both showed that some antipsychotics (including Zyprexa) were superior to haloperidol. The data on file (12 month date from SOHO) supported this view. The fact that aripiprazole was not included in the SOHO study, as it was not available at the time the study started, was not relevant. No specific claim was made versus aripiprazole in the mailer at issue. Lilly believed that to show data from two very different data sets was appropriate to demonstrate the effects of Zyprexa versus a number of antipsychotics. By the very nature of the data sets the measurements used were different. This was actually the whole point that there was consistency even when using an alternative trial approach.

Lilly stated that the validity of the results obtained from observational studies versus those from randomised controlled trials had been widely debated in the scientific literature. Concato *et al* (2000)

discussed the relative position of these types of trial in the hierarchy of research designs and concluded 'The results of well-designed observational studies (with either a cohort or a case-control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomised, controlled trials on the same topic'. In an editorial on this subject Ioannidis *et al* (2001) performed a correlation analysis on the combined databases from Concato *et al* and Benson *et al* (2000) and found that the correlation coefficient between the odds ratio of the randomised controlled trials and the odds ratio of observational designs was 0.84 ($p<0.001$). This represented excellent concordance and was better than that observed when the results of small randomised trials and their meta-analyses were compared with the results of large randomised trials. It was therefore wholly appropriate to compare the results of randomised controlled trials with the outcomes from observational studies to allow clinicians to decide for themselves how generalisable the efficacy data obtained from randomised controlled trials were.

Lilly was aware that NICE [National Institute for Clinical Excellence] Guidance of June 2002 stated in section 6 'Further Research', '6.3 In view of the inability of interventional studies to provide answers to many of the key questions concerning the effects of atypicals, more high quality observational studies are required. In addition, observational studies would provide information on the use of atypicals in individuals with comorbidities and substance abuse disorders'. Lilly did not accept that the SOHO bar chart and bullet point were misleading and found it difficult to understand how they might be construed as disparaging aripiprazole.

Lilly submitted that, in summary the Davis meta-analysis was an independent piece of research with findings consistent with those from the SOHO study and whose conclusions had been accurately reported. The Cochrane review of aripiprazole, a well respected independent meta-analysis, reached conclusions consistent with Davis *et al*. Based on the above arguments Lilly did not accept that it had breached Clauses 7.2, 7.8 or 8.1.

PANEL RULING

The Panel noted that immediately beneath the table of data reporting the findings of the Davis *et al* meta-analysis was the claim at issue 'The results of this meta-analysis are consistent with those observed in SOHO …'. One of the results reported from the meta-analysis was that aripiprazole was equivalent to haloperidol. Aripiprazole, however, was not included in the SOHO study and so in that regard the findings of the two studies could not be consistent. The Panel considered that the claim was thus inaccurate in that regard. A breach of Clause 7.2 was ruled which was appealed by Lilly. The Panel did not consider that the claim at issue disparaged aripiprazole as alleged. No breach of Clause 8.1 was ruled.

APPEAL BY LILLY

Lilly noted that the data was derived from an observational study called SOHO. The NICE Technology Appraisal Guidance No. 43 recommended in section 6 'Further Research' subsection 6.3 'In view of the inability of interventional studies to provide answers to many of the key questions concerning the effects of atypicals, more high quality observational studies are required.' Lilly submitted that this was because randomised controlled trials had strict inclusion and exclusion criteria and demanded that subjects follow a rigid protocol. Such trials had problems, particularly in psychiatry, with large numbers of drop outs and faced criticism that they studied an unrepresentative population. Observational studies provided information on the effectiveness of medicines when used in a 'real world' setting. However, they had the weaknesses that they were unrandomised and open label and so prone to allocation bias and observer bias. The most robust way of considering the type of data generated by these two methods of studying efficacy and effectiveness of medicines was to compare the outcomes of the different trial methodologies. If both methods produced similar results the observer could have greater confidence that their conclusions were valid.

Lilly noted that the SOHO results for 12 months' monotherapy completers suggested that olanzapine produced a greater response rate than oral typicals. The bar chart in the mailer was intended to illustrate that this result matched the results of Davis *et al*. Davis *et al* found that some second-generation antipsychotics were more efficacious than first-generation antipsychotics and others were not significantly different. The bar chart showed that olanzapine and risperidone, medicines found by Davis *et al* to have greater effect sizes than first-generation antipsychotics, also had a greater response rate than oral typicals in an observational study. Quetiapine, a medicine not found by Davis *et al* to be significantly different to first-generation antipsychotics, also had a response rate no higher than oral typicals in SOHO. The concordance of the results of the two methods of studying clinical effectiveness of medicines gave greater confidence in the validity of the results. The results of Davis *et al* and SOHO had not contradicted each other and could therefore be said to be consistent. The mailer did not claim that the results of the two studies were identical, simply that they were consistent. Lilly alleged that it was not misleading to state that the results of Davis *et al* were consistent with SOHO. The statement complained of related to the consistency of the two studies at a general level. The fact that aripiprazole data from SOHO was not yet available was irrelevant.

Aripiprazole was not licensed in Europe when the SOHO observational study started, therefore no patients had initiated the medicine at the start of the observation period and aripiprazole had not appeared in the first 12 month monotherapy completer cohort. Since the mailer was intended to demonstrate that olanzapine had superior efficacy and clinical effectiveness than typical antipsychotics, the lack of clinical effectiveness data from SOHO for aripiprazole was not relevant.

Lilly noted that the complainants also made the point that the data displayed from SOHO was Clinical

Global Rating (CGI) symptoms whereas Davis *et al* examined a variety of measures of clinical efficacy. This was not strictly accurate. The SOHO data was presented as percentage of patients responding in terms of a defined improvement in CGI positive symptoms. Davis *et al* calculated an effect size from the primary end point of the studies analysed, which included PANSS score, BPRS or Clinical Global Rating (the CGI). It would be possible to present the SOHO data as an effect size, but the CGI positive symptoms was one of the main pieces of data collected. The defined improvement in CGI positive symptoms was a measure that clinicians were familiar with and treatment of positive symptoms of schizophrenia was one of their main treatment goals. The data from the two studies were qualitatively similar and had not contradicted each other. Indeed the results of Davis *et al* were presented in an ordinal format. It was therefore not misleading to describe the two sets of data as consistent.

In conclusion, Lilly submitted that the SOHO bar chart at issue had presented data that was fair, balanced and consistent with the results of the Davis *et al* meta-analysis. The company denied a breach of Clause 7.2.

COMMENTS FROM BRISTOL-MYERS SQUIBB AND OTSUKA

The companies noted that they had complained about this claim because aripiprazole was not included in SOHO study, and in this regard data from Davis *et al* could not be consistent with the SOHO results. Thus the companies agreed with the Panel ruling that Lilly was in breach of Clauses 7.2.

The companies noted that Lilly's appeal against this ruling focussed on several points. Firstly, Lilly defended the use and the relevance of observational studies such as SOHO. Secondly, Lilly commented on the similarities between Davis *et al* and the SOHO results with regards to medicines other than aripiprazole, and thirdly Lilly noted that aripiprazole was not included in the SOHO study due to the licensing dates of aripiprazole. The companies did not dispute these points, but did not consider that they were relevant to the complaint or the ruling. The complaint and ruling related to the fact that aripiprazole was not included in the SOHO study and as such it could not be inferred that the Davis *et al* results and SOHO results were consistent with respect to aripiprazole.

Finally, the complainants noted that Lilly had claimed that the intention of the mailing was to demonstrate that olanzapine had superior efficacy and clinical effectiveness than typical antipsychotics. If this was the case, then this intention could have been articulated in a way that did not imply that aripiprazole was included in the SOHO study.

In conclusion, the companies were in agreement with the Panel ruling.

APPEAL BOARD RULING

With regard to the claim 'The results of this meta-analysis are consistent with those observed in SOHO, …' the Appeal Board noted that whilst Davis *et al* analysed aripiprazole data, aripiprazole was not included in the SOHO study and so in that regard the findings of the two studies could not be consistent. The Appeal Board considered that the claim was thus inaccurate 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.

B Discussion aid 'Considering the options in acute schizophrenia' (ref ZY2350)

COMPLAINT

Bristol-Myers Squibb and Otsuka complained that in the table on page two the features of the antipsychotics under review (Zyprexa, risperidone, quetiapine and aripiprazole) appeared to have been selected such that Zyprexa had an entirely positive profile. The complainants did not consider this to be a balanced, fair and objective piece of information.

The points on the left hand side of the table were indicated to list aspects beneficial to short-term and long-term treatment with antipsychotics. However, the only features brought out were those which were beneficial and associated with Zyprexa. Features beneficial to other antipsychotics (eg weight neutrality, lack of sedation) were not mentioned. Further confusion was added by the fact that the Zyprexa data referred to both the oral and the rapid acting intramuscular (IM) formulations. It was not clear that this discussion aid pertained to both formulations: the complainants considered the reader could easily understand from the piece that oral Zyprexa 'begins to reduce positive symptoms within two hours' when in fact this was a property pertaining to IM olanzapine.

Overall the complainants considered that the table was unbalanced, did not conform to the letter and spirit of the Code and disparaged aripiprazole, in breach of Clauses 7.2, 7.8 and 8.1 of the Code.

RESPONSE

Lilly noted that the title of the discussion aid referred to 'acute' schizophrenia and the claim on page 2 made it clear that Lilly was referring to features that were specifically important towards the start of treatment. Thus the features supported the use of Zyprexa from day one. As such, of the ten features listed, four were specific to IM therapy. The list was not meant to be exhaustive but reflected specific features of antipsychotics when used predominantly for acute control of symptoms. Features that were strongly supportive for Zyprexa (such as a lower propensity to cause hyperprolactinaemia and a lower incidence of sexual dysfunction related side effects than some atypicals) were also not listed, nor were features relating to glucose, as these were features of longer-term treatment. Other features which might be favourable for Zyprexa over the longer-term (including improvements in negative, cognitive and depressive features) versus other atypicals had also not been included in this table. The specific features listed by the complainants that might be 'beneficial to

other antipsychotics' (weight neutrality and sedation) might be viewed differently in an acute setting. Indeed, Lilly was not aware of weight neutrality being associated with any antipsychotic and following the recent Case AUTH/1623/8/04, not with aripiprazole. Sedative properties in an acute treatment setting might even be a useful short-term feature.

The combination of oral and IM Zyprexa in this table was in accordance with prescribing information on the item. The use of prominent asterisks made it clear which features were specifically associated with and applied to usage of IM Zyprexa. Lilly did not consider that the reader would have difficulty in noting that the prominent asterisk next to the positive symptoms claim referred to IM use only.

In summary the table reflected predominantly features of antipsychotics that were relevant for the acute treatment of schizophrenia. Where a feature was related to IM use this was made very clear by the use of asterisks. Lilly did not consider the table to be unfair or unbalanced and thus denied breaches of Clauses 7.2, 7.8 or 8.1 of the Code.

PANEL RULING

The Panel noted that the discussion aid was entitled 'Considering the options in **acute** schizophrenia'. The inside pages of the discussion aid started with the question 'Which antipsychotic offers you dependable control from the start?' and ended with the statement 'You can depend on Zyprexa to help you manage schizophrenia from day 1'. Although one of the attributes listed for Zyprexa was 'Effective in the long term' this was presented as a reason for starting the medicine in the first place. The Panel considered that it was clear that the discussion aid was about the initial treatment of schizophrenia and not its long-term management. In that regard the Panel considered that the list of criterion were not inappropriate. As submitted by Lilly, weight neutrality was not an issue in the initial treatment of schizophrenia and sedation as a side-effect could be useful in the initial stages of an acute attack. The Panel thus did not consider that the discussion aid was misleading in that regard and ruled no breach of Clauses 7.2 and 7.8 of the Code. The Panel did not consider that the discussion aid disparaged aripiprazole. No breach of Clause 8.1 was ruled.

The Panel noted that the discussion aid promoted Zyprexa the brand and not a particular formulation of the medicine. Zyprexa was available to be administered orally or as an intramuscular injection. One feature of treatment was listed as 'Rapid-acting IM formulation', for which there was a tick for Zyprexa and a cross for the other atypicals. It was thus clear about which formulation of Zyprexa was being referred to. Two other features ie 'Indicated for rapid control of agitation and disturbed behaviours' and 'Reduces agitation with 15 minutes' (both with a tick for Zyprexa and a cross for the others) were, however, followed by an asterisk which referred the reader to the footnote 'Rapid-acting IM formulation' which appeared in small print beneath the main visual. The Panel considered that, as presented, the claims were unqualified and relied upon the reader to refer to a footnote in order to fully understand the context in which the claims were made. The supplementary information to Clause 7 stated 'It should be borne in mind that claims in promotional material must be capable of standing alone as regards accuracy etc. In general claims should not be qualified by the use of footnotes and the like'. The Panel thus considered that, as depicted, the table was misleading. Breaches of Clauses 7.2 and 7.8 were ruled. The Panel did not consider that the data disparaged aripiprazole. No breach of Clause 8.1 was ruled.

Complaint received **24 September 2004**

Case completed **26 January 2005**

CASE AUTH/1635/9/04

ASTRAZENECA v GLAXOSMITHKLINE

Promotion of Seretide

AstraZeneca alleged that the messages in GlaxoSmithKline's promotional campaign for Seretide (salmeterol/fluticasone) on a theme of total control of asthma, based upon the results of the GOAL (Gaining Optimal Asthma controL) study, were misleading, exaggerated and raised unrealistic expectations. AstraZeneca had a number of concerns regarding the methodology of the GOAL study and considered that GlaxoSmithKline's materials emphasised the results for Seretide and did not put the whole study into context. Total control in the study was defined as meeting the following criteria for at least seven out of eight consecutive weeks: no daily symptoms; no night-time awakenings due to asthma; no exacerbations; no use of rescue medicines; no emergency visits; a peak flow > 80% of predicted in the morning and no treatment-related adverse events forcing a change in therapy. Total control was achieved through Seretide in only 31% and 41% of patients across all strata after dose escalation and at 1 year respectively. This was by no means the majority of patients in the Seretide treatment arm. AstraZeneca considered that the presentation of the promotional material at issue, in which the Seretide logo was used prominently, was such that readers would assume that total control, as defined in the study, and total control of asthma were one and the same thing. Readers would thus associate total control of asthma with Seretide.

Page 4 of a detail aid entitled 'There's no such thing as part freedom' was headed 'This is total control' and featured a table listing all of the components of total control as defined in the GOAL study. Page 5 was headed 'What could total control mean for you and your patients?' and listed, *inter alia*, 'Not having to take your blue inhaler'. A banner running along the bottom of the two pages repeated the requirements for total control and included the Seretide logo. AstraZeneca noted its comments above. The suggestion that total control should be the aim for all asthmatics was contrary to the data eg 10% of patients in the study had drug related adverse reactions. Patients on Seretide must have a reliever inhaler; not taking it was unrealistic and out of licence.

The Panel considered that the information about the GOAL study on page 4 was an integral part of the promotion of Seretide. The description of total control in the context of page 5 which implied that patients on Seretide could achieve total control and change their lives and the information in the banner would be read as implying that Seretide provided total control of asthma as alleged. This was not so. The Panel did not accept GlaxoSmithKline's submission that the total control referred to on these pages related to the definition in the GOAL study. Readers would not appreciate the subtle difference. The Panel considered that in this regard pages 4 and 5 were misleading and exaggerated and not capable of substantiation. Breaches of the Code were ruled. The Panel did not consider it necessarily unreasonable to aim for the composite endpoint of total control even in the situation where the overall incidence of adverse events in the GOAL study was 10%. No breach of the Code was ruled. [These rulings were repeated with regard to: two insert cards for the detail aid; the left hand page of a poster headed 'Total control'; two leavepieces entitled 'Asthma control should be about completely, not partly' and 'Why use Seretide rather than individual components'; a leavepiece item containing a row of post-it notes and GlaxoSmithKline's exhibition stand at the European Respiratory Society Congress.]

The Panel noted that the Seretide SPC stated that patients should be advised to have a reliever, for use in an acute asthma attack, available at all times. Health professionals were extremely familiar with the use of reliever and preventer medicines; the mention of an aim to have no rescue salbutamol use was not unreasonable. However the Panel considered that the claim in the detail aid, 'Not having to take your blue inhaler', went beyond the aim of no rescue salbutamol use. The implication that Seretide patients would not have to take their blue inhaler was inconsistent with the SPC. A breach of the Code was ruled.

Page 6 of the detail aid was headed 'With Seretide you can achieve total control' and featured two bar charts; one depicting the results of the AIRE survey where only 5% of asthma patients achieved guideline-defined asthma control and the other showing the percentage of patients achieving total control in the GOAL study (fluticasone 28%; Seretide 44%). A footnote stated that the two studies were not of comparable design. AstraZeneca alleged that the identical artwork and positioning of the two bar charts, however, misled the audience to conclude that Seretide addressed the gap identified by the patients in the AIRE survey.

The Panel considered that the layout of the pages at issue encouraged readers to directly compare the control seen in AIRE with that in GOAL. The footnote was not sufficient in this regard; misleading material should not be qualified by a footnote. A breach of the Code was ruled.

AstraZeneca alleged that the claim 'Seretide is the only combination to have demonstrated total control as defined by the GOAL study', on page 8 of the detail aid, was misleading and could not be substantiated.

The Panel noted that the only combination used in the GOAL study was Seretide. This was different to the claim which implied that all combination products had been studied and Seretide was the only one that had shown total control. This was not so. Breaches of the Code were ruled. [These rulings were repeated with regard to a similar claim which appeared in a leavepiece entitled 'Asthma control should be about completely, not partly'.]

AstraZeneca complained about a poster which was, in effect an A4 double page spread. The left hand page was headed 'Total control' and the right hand page was headed 'BTS/SIGN adult asthma

guideline'. AstraZeneca's comments and the Panel's rulings with regard to the page headed 'Total control' were as set out above. In addition AstraZeneca stated that although the section headed 'BTS/SIGN adult asthma guideline' had been reproduced with the permission of BTS/SIGN the layout of the page and the branding misleadingly suggested that BTS/SIGN endorsed both total control and Seretide.

The Panel considered that although it could be argued that there was a visual link between total control with Seretide and the BTS/SIGN guidelines, on balance it did not consider that the poster implied that BTS/SIGN endorsed total control and/or Seretide. No breach of the Code was ruled.

With regard to a section headed 'Aim for total control', in a leavepiece entitled 'Why use Seretide rather than individual components?', AstraZeneca noted that there was no indication of the unremarkable percentage of patients that achieved total control on Seretide.

Once again the Panel considered that readers would be left with the impression that Seretide provided total control of asthma which was not so. Breaches of the Code were ruled. With regard to an allegation that information about side-effects or safety had been misleading the Panel noted that there was no mention of these aspects of therapy. No breach of the Code was ruled.

AstraZeneca stated that its arguments set out above also applied to a one page leavepiece 'Reviewing your asthma patients is part of the GMS contract'. The leavepiece listed the features of total control as defined in the GOAL study and gave a list of questions to ask asthma patients to assess whether they were currently achieving total control. AstraZeneca alleged that asking the questions to ascertain if patients were achieving control suggested that Seretide could address this need.

The Panel considered that the description of total control in the context of a page including the Seretide logo would be read as implying that Seretide provided total control of asthma which was not so. Breaches of the Code were ruled. Once again the Panel did not consider it necessarily unreasonable to aim for the composite endpoint of total control. No breach of the Code was ruled in that regard.

AstraZeneca UK Limited complained about the promotion of Seretide (salmeterol/fluticasone) by GlaxoSmithKline UK Limited. A number of items were at issue.

a) Detail aid: 'There's no such thing as part freedom' (ref SFL/DAP/04/13896/1-FP/August 2004) and its insert cards 'GOAL Study' (ref SFL/DAP/04/13896/1a-FP/August 2004) and 'Straight to purple' (ref SFL/DAP/04/13896/1b-FP/August 2004)

b) Poster: 'Total control BTS/SIGN adult asthma guideline' (ref SFL/LVP/04/11425/1-FP/February 2004 20531613)

c) Leavepiece: 'Why use Seretide rather than individual components?' (ref SLF/ LVP/04/11431/1-FP/March 2004 20531627)

d) Leavepiece: 'Reviewing your patients is part of the GMS contract' (ref SFL/LVP/04/12911/1-May 2004)

e) Leavepiece: 'Asthma control should be about completely, not partly' (ref SFL/LVP/04/11426/1-FP/March 2004 20531616)

f) Leavepiece item (ref LOM/CT4/04/11671/1 February 2004 20539404)

g) Exhibition panel at the European Respiratory Society Congress – September 2004

General comments by AstraZeneca

AstraZeneca explained that GlaxoSmithKline was currently promoting Seretide through an extensive and widespread campaign on a theme of total control of asthma. The campaign involved materials to primary care, secondary care and nurses. It was also conveyed on exhibition stands at meetings. The theme of total control of asthma drew upon the recently published GOAL (Gaining Optimal Asthma ControL) study, (Bateman *et al* 2004). AstraZeneca alleged that the resulting messages were misleading, exaggerated and raised unrealistic expectations of Seretide. Such activity was irresponsible and could lead to undesirable effects on asthma patient care.

The GOAL study had its limitations. Results for Seretide patients achieving total control were unremarkable. Therefore the study and its results could not substantiate the misleading messages contained within the campaign

AstraZeneca provided a copy of an online publication which gave an account of the GOAL study. AstraZeneca considered that the following points were particularly relevant:

- The clinical objective for this study was to ascertain if a particular level of control was achievable. However, the messages implied in the materials were misleading in interpreting the data on the amount of control that was actually achieved.
- GOAL was set out as a comparative study between Seretide and fluticasone whereas the materials emphasised results from the Seretide arm and did not put the comparison into context.
- Total control was achieved through Seretide in only 31% and 41% across all strata after dose escalation and at 1 year respectively. This was by no means the majority of patients in the Seretide treatment arm.
- The abstract stated, 'This study confirms that the goal of guideline-derived asthma control was achieved in the majority of patients'. It did not state 'the majority of patients on Seretide'.
- The dosing regimen in both treatment arms across all strata was one of dose escalation and not stepping down. This was contrary to the SIGN/BTS guidelines on management of asthma. These current guidelines clearly set out an objective to achieve and maintain control at the lowest effective dose. Clinical translation of the

results were therefore of questionable value and raised considerable doubt when presented or implied in promotional materials.

- Stratum 1 in the GOAL study included steroid naïve patients who had been put onto Seretide. This was strictly outside the current UK summary of product characteristics (SPC) for Seretide. Any claim that relied on the data from this stratum wholly or in part was misleading.
- The primary objective was to determine the proportion of patients who achieved well-controlled asthma with Seretide compared to fluticasone alone in phase I. This was not mentioned in the promotional materials that focused almost exclusively on total control.
- The incidence of drug related adverse events was 10% in both treatment arms. This was relevant when presenting the aims of treatment set out by the Global Initiative for Asthma (GINA), GOAL data and Seretide branding together in the same item.
- Clinical implications of the unremarkable total control data were misrepresented in the materials. The discussion in the paper stated 'In clinical practice, the decision on whether to aim for Total Control in patients who have reached a lesser level of control, when this involves doubling the dose of controller treatment will need to be made on an individual basis, in consultation with the patient'.

The strong association between total control of asthma and Seretide suggested by the materials was misleading, exaggerated and incapable of substantiation

All the materials in question contained very obvious Seretide branding throughout and were related to, and promoted Seretide.

Total control appeared within all of these items which were very clearly asthma related and promoted an asthma medicine. Therefore it was extremely likely that the reader would conclude that total control and total control of asthma was one and the same thing. It was inconceivable that any reader would view the two as separate entities. Any clarifying caveats were wholly insignificant and unhelpful in comparison to the heavy branding that also appeared.

The clear impact of this execution within the materials was that the audience was misled into associating total control of asthma with Seretide. As such, this raised unreasonable and unfounded expectations that prescribing Seretide would deliver a good chance of attaining total asthma control in the majority of patients. AstraZeneca alleged this to be highly misleading and irresponsible:

- Highlights from the publication as set out above clearly pointed out that the majority of patients on Seretide did not achieve total control. Only 41% across all strata achieved this level of control.
- This figure included the out of licence stratum 1 (steroid naïve patients).
- The cumulative figures for strata 2 and 3 were 44% and 29% respectively at the end of phase 2 with only incremental further benefits in phase 3 (oral steroids and highest dose of Seretide).
- Progressive stepping up of therapy without stepping down was outside of current UK practice guidelines (SIGN/BTS).

The results for Seretide patients achieving control were unremarkable and incapable of supporting the clear association made between total control and Seretide.

General comments from GlaxoSmithKline

GlaxoSmithKline explained that the GOAL study was the first prospective clinical trial to assess whether National Institute of Health (NIH)/GINA guideline-defined asthma control could be achieved with current established treatments.

The GOAL study authors defined two new levels of asthma control, based upon the NIH/GINA Guidelines: well-controlled (the primary endpoint) and total control. Both of these were composite measures, used to evaluate treatment effectiveness and required control to be achieved and sustained for at least seven out of an eight-week period.

Rationale for the GOAL trial

Clinical trials had traditionally measured the efficacy of asthma treatments by assessing changes in a single endpoint eg peak expiratory flow (PEF) or forced expiratory volume (FEV) or the use of rescue medications. However, single variables could provide an incomplete assessment of disease control and could over-estimate the degree of asthma control achieved (Clarke *et al* 2002). A composite measure gave a more meaningful and accurate assessment of control. The GOAL study evaluated how many patients reached the two levels of control, well-controlled and total control.

Trial design

GlaxoSmithKline explained that the GOAL study was an international, multi-centre, stratified, randomised, double-blind, parallel-group, step-up clinical trial, designed to determine what proportion of patients could achieve asthma control with Seretide (salmeterol/fluticasone combination) or Flixotide (fluticasone) alone in adults and adolescents. 3416 uncontrolled asthmatics, were randomised in the one-year trial. Treatment was stepped up every 12 weeks, if necessary, until either total control was achieved or the maximum dose of inhaled corticosteroid was reached (phase I). This phase was followed by a maintenance dose phase (phase 2), so that the total double-blind period was 52 weeks. Control was assessed over the last eight weeks in each twelve-week step-up period. The patients were enrolled from 326 sites in 44 countries and recruited based on dose of inhaled corticosteroid at study entry.

Total control was defined as meeting the following criteria for at least seven out of eight consecutive weeks:

- No daily symptoms
- No night-time awakenings due to asthma

- No exacerbations
- No use of rescue medications (salbutamol)
- No emergency visits
- A peak flow greater than 80% of the predicted value, measured in the morning
- No treatment-related adverse events forcing a change in asthma therapy.

Well-controlled was defined by the authors as meeting the following criteria every day for at least seven out of eight consecutive weeks:

- No night-time awakenings due to asthma
- No exacerbations
- No emergency visits
- No treatment-related adverse effects forcing a change in asthma therapy

AND two or more of the following:

- Symptoms on no more than 2 days with a symptom score of greater than 1
- Use of rescue medication (salbutamol/albuterol) between 2 and 4 days a week
- A peak flow greater than 80% of the predicted value, measured in the morning.

5068 patients were screened for inclusion in the study. 3421 patients, who were defined as uncontrolled in the run-in period, were suitable for randomisation.

Patients were stratified, according to their inhaled corticosteroid dose in the previous 6 months: stratum 1: no inhaled steroid ('steroid-naïve'); stratum 2: ≤ 500mcg beclomethasone diproprionate daily or equivalent; stratum 3: > 500 – ≤ 1,000mcg beclomethasone diproprionate daily or equivalent. Each stratum was randomised to the dose of Seretide or fluticasone most appropriate to their previous treatment in the past 6 months.

Treatment strategies

The trial compared two treatments: Seretide versus inhaled corticosteroid alone. Both treatments were titrated upwards as necessary. When total control was achieved the patient was maintained on that dose until the end of the year long study. This allowed the study to determine which treatment achieved and maintained total control more successfully. The study also determined the time to achieve control, and the dose of inhaled corticosteroid at which this was achieved. The safety of these treatments using this treatment strategy was also monitored.

Key findings

This was the first study to demonstrate that:

- guideline-defined asthma control (well-controlled), the primary endpoint of this study, could be achieved in the majority using standard current treatment options; 71% of patients across the three strata achieved this level of asthma control.
- that an even higher level of asthma control, first defined within this study as total control, could also be achieved. With sustained treatment 50% of patients in stratum 1, 44% in stratum 2 and 28% in stratum 3 achieved it.

GlaxoSmithKline noted that feedback from opinion leaders in respiratory medicine did not confirm AstraZeneca's view that the results of the GOAL study were unremarkable. In fact, as the first randomised controlled trial of this size and design, involving 44 different countries around the world, it had received feedback that the GOAL study truly was a landmark clinical trial in respiratory medicine. One UK investigator had commented, 'I think the GOAL study results have major implications for the way we manage asthma. It's saying, 'we can't accept limited lifestyles, we can't accept asthma attacks, we can't accept these level of symptoms anymore'. We can achieve so much more for people with asthma – the vast majority of people can lead a normal life'.

A Detail aid: 'There's no such thing as part freedom'

1 Pages 4 and 5 double page spread

Page 4 was headed 'This is total control' and featured a table listing the requirements for total control as defined in the GOAL study. Beneath the table was the statement 'Total control should be the aim for all your asthma patients' which was referenced to the GOAL study. Page 5 was headed 'What could total control mean for you and your patients?' and listed, *inter alia*, 'Not having to take your blue inhaler'. A banner running along the bottom of the two pages repeated the requirements for total control. These being 'No daytime symptoms. No rescue salbutamol use. No days at <80% AM PEF. No night-time awakening. No exacerbations. No emergency hospital visits. No adverse events leading to treatment change. For at least 7 out of 8 weeks as defined by the GOAL Study'. The reference to 7 out of 8 weeks appeared in much smaller type below the banner.

COMPLAINT

AstraZeneca noted that the banner across the bottom, listing the features of total control included the Seretide logo as an integral feature. All the contents of this double page were therefore strongly associated with Seretide. AstraZeneca applied all the arguments set out in its general comments above to this double page. The suggestion that total control should be the aim for all asthma patients was contrary to the data eg 10% of patients in the study had drug related adverse events. Patients on Seretide must have a reliever (blue) inhaler; not taking it was therefore unrealistic and out of licence.

AstraZeneca alleged the double page spread breached Clauses 3.2, 7.2, 7.4, 7.9 and 7.10.

RESPONSE

In relation to the banner, GlaxoSmithKline submitted that the definition of total control had been factually represented across the bottom of each page to remind the reader of the endpoints which constituted total control. This reinforced the message that total control

referred to the definition outlined in the GOAL study, rather than a non-specific reference to total control of asthma. In addition the time period over which this was assessed had been given as 7 out of 8 weeks. The Seretide logo at the bottom far right corner of page 5 was of appropriate prominence and no claim was made for Seretide.

In relation to the arguments set out in AstraZeneca's general comments as they applied to this page GlaxoSmithKline agreed that this was clearly Seretide promotional material, but considered the level of branding to be appropriate.

AstraZeneca's comment that total control and total control of asthma was one and the same thing.

On the first page, 'This is total control', an entire page had been dedicated to explicitly defining the GOAL study definition of total control. GlaxoSmithKline had taken considerable care in ensuring that the definition of total control was given clearly and early within the detail aid to ensure that the reader was not misled. At no point had the phrase total control of asthma been used within the detail aid or any other materials. It was made clear that total control referred to the definition given within the GOAL study, which was fully referenced. It was not a non-specific reference to total control of asthma as suggested.

Association between total control of asthma with Seretide

No claim regarding Seretide and total control of asthma had been made in any of the Seretide materials. Great care had been taken in the execution of the materials, to highlight that patients achieved a new level of asthma control, total control (as defined in the GOAL Study) using Seretide. GlaxoSmithKline did not consider that the reader would be misled into associating Seretide with total control of asthma.

- **41% across all strata achieve total control**

GlaxoSmithKline noted that AstraZeneca had alleged that the materials raised unreasonable expectations that there was a good chance of achieving total control of asthma in the majority of patients. It was important to recognise, once again, that the materials made no reference to total control of asthma. However, retrospective analysis of previous Seretide studies, estimated that only 15% of patients would achieve this level of asthma control, total control, as set out in the GOAL study. The GOAL study had shown that 41% of patients across all three strata achieved total control. This was therefore a highly significant and remarkable finding. A significant percentage achieved total control and by aiming for total control, 71% of patients across all three strata achieved guideline-defined asthma control.

- **Out of licence data**

GlaxoSmithKline noted that AstraZeneca had alleged that the materials were misleading because the 41% figure included out of licence stratum 1 data. However, none of the materials at issue had reported the 41% figure. The data shown referred to strata 2 and 3 for which Seretide was licensed.

- **Cumulative figures for strata 2 and 3 are 44% and 29% at the end of phase 2 with only incremental further benefits in phase 3 (oral steroids and highest dose of Seretide).**

GlaxoSmithKline noted that AstraZeneca had alleged that the materials raised unreasonable expectations of patients in strata 2 and 3. AstraZeneca was correct in reporting the figures for those achieving total control after sustained treatment in strata 2 and 3 for patients randomised to Seretide. However, there was no phase 3 within the GOAL study.

Patients in stratum 2 (previously uncontrolled on low dose inhaled corticosteroids, ie < 500mcg/day beclometasone equivalent) constituted the largest group of asthma patients in the UK. For this group up to 44% achieved total control. Moreover, by aiming for this level of asthma control 75% achieved guideline-defined asthma control.

Patients in stratum 3 (> 500 < 1000mcg/day of inhaled corticosteroid) represented the more severe spectrum of asthma patients within the UK. For these patients achieving a level of asthma control equivalent to total control (in the GOAL study) was beyond expectations. Therefore, for 29% of these to achieve this level of asthma control was truly remarkable. Moreover, by aiming for this level of asthma control, 62% achieved guideline-defined asthma control.

- **Outside current UK practice guidelines**

Contrary to AstraZeneca's complaint GlaxoSmithKline submitted that that the treatment strategy of the GOAL study was in line with the current BTS/SIGN recommendations, which recommended starting patients on the most appropriate dose for the severity of their disease and achieving and maintaining control. The guidelines recommended stepping down only when adequate control was achieved. In the accompanying editorial for the GOAL study, a member of the BTS/SIGN Asthma Guidelines Steering Committee, commented that the implications were that disease control improved slowly and that stepping down should occur after 3-6 months. He stated that the study was consistent with guidelines.

Total control should be the aim for all asthma patients

The GOAL study had shown that a new and higher level of asthma control, than previously seen within any clinical study, could be achieved. By aiming for total control, the majority of patients (64% in stratum 2) achieved a quality of life that approached near-maximal levels (> 6).

This study had therefore reset expectations for both patients and health professionals of what could be achieved in asthma management. The authors of the GOAL study had endorsed this inspirational statement, stating that total control should be the aim for all asthma patients, because the study had shown that it was achievable in a considerable proportion of patients (41% across all strata). By aiming for total control, within the GOAL study, considerable benefits were achieved in almost all patients.

GlaxoSmithKline noted that AstraZeneca had stated that total control should not be the aim for all asthma

patients, because 10% of patients in the study had drug related adverse events. The definition of an adverse event applied to clinical trials was any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product which did not necessarily have a causal relationship with this treatment. The figure of 10% was therefore a factual representation of all events defined above. In fact the overall frequency and nature of self-reported adverse events were similar to other trials involving inhaled corticosteroids in asthma and predominantly affected the upper respiratory tract [oral candidiasis (3%), hoarseness (3%) and pharyngolaryngeal pain (< 1%)]. These were well recognised side-effects of all inhaled corticosteroids.

GlaxoSmithKline noted that no claim had been made on the safety of Seretide within any of the materials. The only mention of side effects was the definition of total control and well-controlled, which included the endpoint, 'no adverse events leading to a treatment change' (for 7 out of 8 weeks assessed).

Patients on Seretide must have a reliever inhaler

GlaxoSmithKline noted AstraZeneca's comment that not using the blue inhaler was unrealistic and out of licence. The GOAL study had shown that up to 41% of patients across all severities of asthma did not use their reliever inhaler for rescue use for 7 out of 8 weeks. This was not only a remarkable finding, but also realistic for a significant number of patients.

The materials did not recommend that patients should not be using reliever inhalers and no claim had been made. The only mention of reliever use was contained within the definition of total control and well controlled.

GlaxoSmithKline denied any breach of Clauses 3.2, 7.2, 7.4, 7.9 and 7.10.

PANEL RULING

The detail aid clearly promoted Seretide, page 3 was headed 'Seretide – for patients uncontrolled on inhaled corticosteroids alone' followed by an illustration of a beclometasone inhaler and Seretide inhalers. The Panel considered that the information about the GOAL study on page 4 was an integral part of the promotion of Seretide. The Panel considered that the description of total control on page 4 of the detail aid in the context of page 5 which implied that patients on Seretide could achieve total control and change their lives and the information in the banner would be read as implying that Seretide provided total control of asthma as alleged. This was not so. The Panel did not accept GlaxoSmithKline's submission that the total control referred to on these pages related to the definition in the GOAL study. Readers would not appreciate this subtle difference. The Panel considered that in this regard the double page (pages 4 and 5) was misleading exaggerated and not capable of substantiation. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

The Panel noted that one of the relevant endpoints for total control was that for at least 7 out of 8 weeks there were no adverse events leading to a treatment change. The Panel did not consider it necessarily unreasonable to aim for the composite endpoint of total control even in the situation where the overall incidence of adverse events in the GOAL study was 10%. The Panel ruled no breach of Clause 7.9 of the Code.

The Panel noted that the Seretide Accuhaler SPC stated that patients should be advised to have their medicinal product to be used for relief in an acute asthma attack available at all times (Section 4.4). Health professionals were extremely familiar with the use of reliever and preventer medication. The mention of an aim to have no rescue salbutamol use was not unreasonable. However the Panel considered that the claim 'Not having to take your blue inhaler' went beyond the aim of no rescue salbutamol use. The Panel considered that the implication that Seretide patients would not have to take their blue inhaler was inconsistent with the SPC. The Panel thus ruled a breach of Clause 3.2 of the Code.

2 Claim 'With Seretide you can achieve total control'

This claim was the heading to page 6 which featured two bar charts; one depicting the percentage of patients controlled according to the AIRE survey where only 5% of asthma patients achieved GINA guideline defined control and the other showing the percentage of patients who achieved total control in the GOAL study; the results being fluticasone (28%) or Seretide (44%). A footnote to the bar charts stated 'These studies are not of comparable design'.

COMPLAINT

AstraZeneca alleged that the identical artwork and positioning of the two bar charts misled the audience to conclude Seretide addressed the gap identified by the patients in the AIRE survey. The caveat was not sufficient to overcome the misleading message conveyed through the execution of the graphs. A breach of Clause 7.2 was alleged.

RESPONSE

GlaxoSmithKline stated that the first bullet at the top of this page referred to the percentage of patients achieving GINA guideline-defined control in the AIRE survey (5%). The second bullet referred to the percentage of Seretide-treated patients achieving total control as defined in the GOAL study (44%). These were clearly two different levels of asthma control, which had been stated explicitly. The two bar charts were titled accordingly as above with a prominent caveat highlighting that the two studies were not of comparable design.

GlaxoSmithKline denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that little information was provided in the detail aid about the AIRE survey and the GINA guideline-defined control.

The layout of the page encouraged readers to directly compare the control seen in AIRE with that in GOAL. The Panel noted that beneath the graphs was the statement 'These studies are not of comparable design'. The Panel did not accept that this was sufficient. It was an established principle under the Code that otherwise misleading material should not be qualified by footnotes. The Panel ruled a breach of Clause 7.2 of the Code.

During its consideration of this allegation the Panel considered that page 6 was similar to pages 4 and 5 in that it implied that Seretide provided total control of asthma. There was no clear allegation in this regard. The Panel requested that GlaxoSmithKline be advised of its concerns.

3 Claim 'Seretide is the only combination to have demonstrated total control as defined by the GOAL study'

This claim appeared as the heading to page 8 of the detail aid.

COMPLAINT

AstraZeneca noted that Seretide was the only combination actually used in the GOAL study and the only combination to have been studied with this specific total control end point. However, the results were unremarkable and had not been declared.

AstraZeneca alleged breaches of Clauses 7.2 and 7.4.

RESPONSE

GlaxoSmithKline stated that there were currently two combination inhalers available – Seretide and Symbicort (budesonide/formoterol). It was factually correct that Seretide was the only combination inhaler which had been shown to achieve total control. GlaxoSmithKline denied a breach of Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that the only combination product used in the GOAL study was Seretide. This was different to the claim which implied that all combination products had been studied and Seretide was the only one that had shown total control. This was not so. The claim was misleading and not capable of substantiation. The Panel thus ruled breaches of Clauses 7.2 and 7.4 of the Code.

4 Insert cards: 'GOAL study' and 'Straight to Purple'

Both cards had a banner running along the bottom edge which listed the criteria for total control as defined in the GOAL study; the Seretide product logo appeared in the bottom right hand corner.

COMPLAINT

AstraZeneca noted that both cards contained the branding banner across the bottom of the pages and therefore warranted consideration as per point A1 above.

RESPONSE

GlaxoSmithKline referred to its comments at point A1 above.

PANEL RULING

The Panel considered that its ruling in point A1 of breaches of Clauses 7.2, 7.4 and 7.10 also applied here.

B Poster: 'Total Control, BTS/SIGN adult asthma guideline'

The poster was, in effect an A4 double page spread. The left-hand page was headed 'Total control' and the right hand page was headed 'BTS/SIGN adult asthma guideline'.

1 Page headed 'Total control'

COMPLAINT

AstraZeneca noted the very obvious Seretide branding on the bottom of the page which came across as an integral feature. All the contents of this page were therefore strongly associated with Seretide. AstraZeneca applied all the arguments set out in its general comments for this item. The suggestion that total control should be the aim for all asthma patients was contrary to the data eg 10% of patients in the study had drug related adverse events.

AstraZeneca alleged breaches of Clauses 7.2, 7.4, 7.9 and 7.10.

RESPONSE

GlaxoSmithKline referred to its response as set out in point A1 above. GlaxoSmithKline denied breaches of Clauses 7.2, 7.4, 7.9 and 7.10.

PANEL RULING

The Panel noted that this page was different to page 4 in the detail aid considered at point A1 above. The page of the poster had different layout and included different claims, and there was no footnote banner as in point A1. Nonetheless the ruling in point A1 was relevant.

The Panel considered that the description of total control on the poster with the claim 'Prescribe Seretide for patients uncontrolled on inhaled corticosteroids (ICS) alone because it is more effective at delivering total control' followed by the Seretide logo would be read as implying that Seretide provided total control of asthma. This was not so. The page was misleading, exaggerated and not capable of substantiation. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

The Panel noted its ruling in point A1 regarding the adverse event data.

The Panel noted that one of the relevant endpoints for total control included in the poster was that for at least 7 out of 8 weeks there were no adverse events leading to a treatment change. The Panel did not consider it necessarily unreasonable to aim for the composite endpoint of total control even in the situation where the overall incidence of adverse events in the GOAL study was 10%. The Panel ruled no breach of Clause 7.9 of the Code.

2 Page headed 'BTS/SIGN adult asthma guideline'

The page set out the BTS/SIGN asthma guideline giving details of steps 1, 2 and 3. With regard to step 1 the poster did not refer to any specific medicines. Beneath the details of step 2 reference was made to beclomethasone or equivalent. Above the details of step 3 reference was made that the addition of an inhaled long-acting beta agonist was the first choice at step 3. There was no mention of Seretide, total control or use of the Seretide logo on this page.

COMPLAINT

AstraZeneca stated that although this section had been reproduced with the permission of BTS/SIGN, the layout of the page together with the branding suggested that BTS/SIGN endorsed both total control and Seretide. AstraZeneca alleged that this was misleading and a breach of Clause 7.2.

RESPONSE

GlaxoSmithKline stated that in keeping with the its policy of sending all materials referencing the BTS/SIGN asthma guideline to SIGN for approval, this material was sent to SIGN who approved the material as presented; a copy of relevant correspondence was provided.

GlaxoSmithKline denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that both pages used similar colour schemes. It could be argued that the poster gave the visual impression that there was a link between total control with Seretide and the BTS/SIGN adult asthma guidelines. On balance the Panel did not consider that the poster implied that BTS/SIGN endorsed total control and or/Seretide. The Panel did not consider the material was misleading in this regard. No breach of Clause 7.2 of the Code was ruled.

C Leavepiece: 'Why use Seretide rather than individual components?'

The leavepiece opened out such that three sections of information 'This is total control', 'Seretide cost comparison' and 'Aim for total control' all became visible at the same time. The Seretide logo appeared at the bottom right of the three page spread ie at the bottom of the section headed 'Aim for total control'.

1 Section headed 'This is total control'

This section detailed the components of total control as defined in the GOAL study.

COMPLAINT

AstraZeneca stated that this section of the leavepiece was strongly associated with Seretide and all of its general comments as set out above applied. The suggestion that total control should be the aim for all asthma patients was contrary to all the data eg 10% of patients in the GOAL study had drug related adverse events. AstraZeneca alleged breaches of Clauses 7.2, 7.4, 7.9 and 7.10 of the Code.

RESPONSE

GlaxoSmithKline stated that although this was clearly a promotional piece, the Seretide branding was appropriate.

In relation to those arguments set out in by AstraZeneca in its general comments GlaxoSmithKline referred to its response as set out in point A1 above. In relation to 'Total Control should be the aim for all asthma patients' GlaxoSmithKline again referred to its response in point A1 above. GlaxoSmithKline denied breaches of Clauses 7.2, 7.4, 7.9 and 7.10.

PANEL RULING

The Panel noted that this section was different to previous items (point A1 and point B1 above). The section at issue would be read in the context of a leavepiece entitled 'Why use Seretide rather than individual components?' which also included the Seretide logo. The ruling in point A1 was relevant. The Panel considered that the section at issue 'This is total control' would be read as implying that Seretide provided total control of asthma. This was not so. The page was misleading, exaggerated and not capable of substantiation. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

The Panel noted its ruling in points A1 and B1 regarding the adverse event data.

The Panel noted that one of the relevant endpoints for total control included in the leavepiece was that for at least 7 out of 8 weeks there were no adverse events leading to a treatment change. The Panel did not consider it necessarily unreasonable to aim for the composite endpoint of total control even in the situation where the overall incidence of adverse events in the GOAL study was 10%. The Panel ruled no breach of Clause 7.9 of the Code.

2 Section headed 'Aim for total control'

This section included an illustration of beclomethasone inhalers and the equivalent Seretide inhalers.

COMPLAINT

AstraZeneca noted that there was no indication of the unremarkable percentage of patients that achieved total control on Seretide. Again this raised unreasonable expectations of Seretide through the misleading layout.

AstraZeneca alleged breaches of Clauses 7.2, 7.4, 7.9 and 7.10.

RESPONSE

GlaxoSmithKline stated that this leavepiece was produced at the start of the promotional campaign, in March 2004, to raise awareness of total control as defined in the GOAL study, rather than presenting detailed results. It also factually presented the cost comparison of Seretide versus its constituents. The leavepiece made no claims for Seretide achieving total control and so GlaxoSmithKline denied any breach of Clauses 7.2, 7.4, 7.9 and 7.10.

PANEL RULING

The Panel noted that this section was headed 'Aim for total control'. It considered however in the context of the leavepiece which stated in the front page 'Why use Seretide rather than individual components?' that readers would be left with the impression that Seretide provided total control of asthma. This was not so. The section was misleading, exaggerated and not capable of substantiation. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

With regard to the alleged breach of Clause 7.9 the Panel noted that there was no mention of adverse effects or safety in the section in question. Thus the Panel ruled no breach of Clause 7.9 of the Code.

D Leavepiece: 'Reviewing your asthma patients is part of the GMS contract'

This one page item started with the Seretide logo followed by the statement 'Reviewing your asthma patients is part of the GMS contract'. This was followed by 'What is total control (as defined in the GOAL study)?' and a list of the features followed by a list of questions to ask asthma patients so as to assess whether they were currently achieving total control.

COMPLAINT

AstraZeneca noted that again the Seretide branding was a prominent and integral part of the page and stated that the arguments set out in its general comments above applied to this item. By asking the questions to ascertain if patients were achieving control, there was a strong misleading suggestion that Seretide could address this need.

AstraZeneca alleged breaches of Clauses 7.2, 7.4, 7.9 and 7.10.

RESPONSE

In relation to branding and AstraZeneca's general comments GlaxoSmithKline referred to its response set out in point A1 above.

In relation to questions to ascertain if patients were achieving control GlaxoSmithKline stated that the questions were designed to enable clinicians to assess the level of asthma control their patients were currently achieving, by assessing asthma control according to a composite measure rather than single endpoints. Research had shown that assessing asthma control on single endpoints alone, such as lung function and/or symptoms, could overestimate the level of asthma control achieved. By providing examples of questions to be used, this item helped health professionals use a structured approach and avoid the use of open questions such as, 'how is your asthma?'.

GlaxoSmithKline denied breaches of Clauses 7.2, 7.4, 7.9 and 7.10.

PANEL RULING

The Panel noted its rulings at point A1 above.

The Panel noted that although this item was different to the page in the detail aid considered at point A1, both items similarly referred to the composite definition of total control in the GOAL study. The Panel considered that the ruling at point A1 was relevant.

The Panel considered that the description of total control on the leavepiece in the context of a page including the Seretide logo and thus promoting that medicine would be read as implying that Seretide provided total control of asthma. This was not so. The page was misleading, exaggerated and not capable of substantiation. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

The Panel noted its ruling in point A1 regarding the adverse event data.

The Panel noted that one of the relevant endpoints for total control included in the leavepiece was that for at least 7 out of 8 weeks there were no adverse events leading to a treatment change. The Panel did not consider it necessarily unreasonable to aim for the composite endpoint of total control even in the situation where the overall incidence of adverse events in the GOAL study was 10%. The Panel ruled no breach of Clause 7.9 of the Code.

E Leavepiece: 'Asthma control should be about completely, not partly'

This was a four page leavepiece. The pages at issue were 2 and 3 which formed the inside double page spread. The Seretide product logo appeared in the bottom right hand corner of page 3.

1 Page 2 headed 'What does asthma control currently mean to you?'

Page 2 featured a table which, in the right hand column, set out the seven endpoints used in GOAL to define total control. The left hand column had 'no' beside each endpoint. An arrow 'This is total control' pointed up at the 'no' column. A flap on the page obscured the no column with another column which listed incidences of the various endpoints. It appeared that the incidences equated with the reader's understanding of 'What does asthma control currently mean to you' (the heading to the page).

COMPLAINT

AstraZeneca considered that its comments at point C1 above applied here.

RESPONSE

GlaxoSmithKline referred to its response at point A1 above.

PANEL RULING

The Panel noted that this page was different to items considered at points C1 and A1. The Panel considered that the leavepiece would be seen as part of the promotion of Seretide. The product logo was included on page 3. Seretide promotional aids were also included (these appeared to be markers for use in patients' notes).

The Panel considered that the description of total control in the leavepiece in the context of the promotion of Seretide would be read as implying that Seretide provided total control of asthma. This was not so. The page was misleading, exaggerated and not capable of substantiation. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

The Panel noted its ruling in A1 and C1 regarding the adverse event data.

The Panel noted that one of the relevant endpoints for total control included in the leavepiece was that for at least 7 out of 8 weeks there were no adverse events leading to a treatment change. The Panel did not consider it necessarily unreasonable to aim for the composite endpoint of total control even in the situation where the overall incidence of adverse events in the GOAL study was 10%. The Panel ruled no breach of Clause 7.9 of the Code.

2 Page headed 'Asthma control should be about completely, not partly'

Page 3 included claims that total control as defined in the GOAL study should be the aim for all asthma patients followed by the claim 'Prescribe Seretide for patients uncontrolled on [inhaled corticosteroid] alone because it is more effective at delivering total control'.

COMPLAINT

AstraZeneca considered that its comments at point A3 applied here.

RESPONSE

GlaxoSmithKline referred to its response at point A3 above.

PANEL RULING

The Panel noted that this item was different to that considered at point A3 above. The ruling on point A3 was, however, relevant. The claim at issue 'Seretide is the only combination to have demonstrated total control' implied that all combination products had been studied and Seretide was the only one that had shown total control. This was not so. The claim was misleading and not capable of substantiation. The Panel thus ruled breaches of Clauses 7.2 and 7.4 of the Code.

F Leavepiece item

This item was a desk pad which contained a row of post-it notes.

COMPLAINT

AstraZeneca noted that the front of this item listed features of total control, contained bullet points and Seretide branding. Again the message associated total control of asthma with Seretide without qualifying the number of patients in the study achieving this objective.

Opening the cover further conveyed the same misleading message through depicting all the presentations of Seretide along with total control post-its and the Seretide branding. AstraZeneca referred to its general comments set out above. The suggestion that total control should be the aim for all asthma patients was contrary to all the data eg 10% of patients in the study had drug related adverse events.

AstraZeneca alleged that page was in breach of Clauses 7.2, 7.4, 7.9 and 7.10.

RESPONSE

GlaxoSmithKline noted that the definition of total control, as defined in the GOAL study, was presented on the front of this item. This was followed with bold bullets reinforcing that this piece referred to total control from the GOAL study, rather than total control of asthma. The objective of the desk pad was to raise awareness of the new level of asthma control that was achieved in the GOAL study, rather than represent the results of the study.

On opening the flap of the desk pad, images of Seretide and beclometasone inhalers were displayed to remind the reader of the different strengths and presentations available and equivalent beclometasone doses. The post-its were watermarked with the definition of total control, given explicitly as before. It was clear from the bullet points below that this referred to total control as defined in the GOAL study rather than a non-specific reference to total control of asthma.

In relation to AstraZeneca's general comments GlaxoSmithKline referred to its response to point A1 above. In relation to the claim that total control should be the aim for all asthma patients, GlaxoSmithKline referred to its response in point A1 above. GlaxoSmithKline denied breaches of Clauses 7.2, 7.4, 7.9 and 7.10.

PANEL RULING

The Panel considered that its rulings at A1 were relevant. Readers would be left with the impression that Seretide provided total control of asthma. This was misleading, exaggerated and not capable of substantiation. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

The Panel noted that one of the relevant endpoints was that for at least 7 out of 8 weeks there were no adverse events leading to a treatment change. The

Panel did not consider it necessarily unreasonable to aim for the composite endpoint of total control even in the situation where the overall incidence of adverse events in the GOAL study was 10%. The Panel ruled no breach of Clause 7.9 of the Code.

G European Respiratory Society (ERS) Congress (Glasgow – September 2004) – Exhibition stand

COMPLAINT

AstraZeneca provided a photograph which it stated showed the strong association between Seretide and total control as promoted at the above meeting. AstraZeneca stated that all the arguments listed in its general comments above applied here.

AstraZeneca alleged breaches of Clauses 7.2, 7.4, 7.9 and 7.10.

RESPONSE

GlaxoSmithKline stated that the panel at the ERS exhibition stand clearly defined total control in the GOAL Study. It displayed factually the seven endpoints, which made up the definition of total control. It was accurately referenced and clearly stated that it referred to the GOAL study.

It was unfortunate that the photograph only displayed a limited view of the entire stand and gave the impression that the large Seretide logo was directly associated with this panel. The stand was considerable in size, as befitted an international meeting and the logo was designed to help delegates identify where the Seretide exhibition stand could be found. The close association between the total control panel and prominent Seretide logo was purely coincidental and exaggerated by the photograph.

GlaxoSmithKline denied breaches of Clauses 7.2, 7.4, 7.9 and 7.10.

PANEL RULING

The Panel noted that it had been supplied with a photograph of the stand by AstraZeneca. No detailed information had been supplied by GlaxoSmithKline.

The Panel considered that its ruling in point A1 was relevant.

The impression from the photograph was that Seretide provided total control of asthma. This was not so. The Panel considered the stand was misleading, exaggerated and not capable of substantiation. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10 of the Code.

The Panel noted its ruling in point A1 regarding the adverse event data.

The Panel noted that one of the relevant endpoints included in the poster was that for at least 7 out of 8 weeks there were no adverse events leading to a treatment change. The Panel did not consider it unreasonable to aim for the composite endpoint 'Total control' even in the situation where the overall incidence of adverse events in the GOAL study was 10%. The Panel ruled no breach of Clause 7.9 of the Code.

Complaint received	**29 September 2004**
Case completed	**19 January 2005**

CASE AUTH/1641/10/04

ROCHE v NOVARTIS

Prescribing information for Myfortic

Roche alleged that Novartis had misled physicians about the safety of the interchangeability of Myfortic (mycophenolic acid) and Cellcept (mycophenolate mofetil), as the Myfortic prescribing information was not consistent with the summary of product characteristics (SPC). Section 4.4 of the Myfortic SPC, Special warnings and precautions for use, stated '[Myfortic] and [Cellcept] should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles'. However, the relevant statement in the prescribing information read: 'Due to different pharmacokinetic profiles care should be taken when interchanging or substituting [Myfortic] and [Cellcept]'. Roche submitted that the intention of the SPC was that the two products should not be interchanged or substituted without good clinical reason whereas the prescribing information implied that it was acceptable to interchange the two as long as care was taken.

The Panel noted that the Myfortic SPC referred to patients being switched from Myfortic to Cellcept and *vice versa*. Although Novartis had submitted that data showed that switching patients from Cellcept to Myfortic was not associated with any deterioration in safety or efficacy, no data was supplied about the conversion of patients from Myfortic to Cellcept.

The Panel noted that an SPC represented the agreed information about a medicine. The Panel considered that there was a material difference between the two statements at issue. The SPC referred to the grounds for changing a patient from one product to the other and implied that such a switch should not be made without good clinical reason. The statement in the prescribing information, however, did not tell doctors of the caution that they must exercise in making the initial decision to switch. In the Panel's view the prescribing information referred to the manner in which patients were managed once the decision to switch had been made. The Panel thus considered that the statement in the prescribing information did not reflect the substance of the relevant information in the SPC as required by the Code. A breach of the Code was ruled.

Upon appeal by Novartis the Appeal Board noted that the statement in the Myfortic SPC that '[Myfortic] and [Cellcept] should not be indiscriminately interchanged or substituted' had been suggested by Novartis and agreed with the regulatory authorities and was slightly unusual in its use of the word 'indiscriminately'. The relevant statement in the prescribing information referred to the need to take care. The Appeal Board also noted that the statement in the prescribing information read 'care should be taken *when* interchanging or substituting [Myfortic] and [Cellcept]' (emphasis added). In the Appeal Board's view 'when' in that statement meant that interchanging or substituting the two products was acceptable provided it was done with care whereas the SPC statement implied that prescribers should be cautious about making the decision to change therapy at all.

The Appeal Board considered that there were important differences between the two statements and upheld the Panel's ruling of a breach of the Code.

Roche Pharmaceuticals complained about the prescribing information for Myfortic (mycophenolic acid) issued by Novartis Pharmaceuticals UK Limited. Myfortic was indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants. Roche marketed Cellcept (mycophenolate mofetil) which, in addition to being licensed for the same indication as Myfortic, could also be used as proplylaxis of acute rejection in cardiac or hepatic transplants.

COMPLAINT

Roche alleged that Novartis had misled physicians with regard to the safety of the interchangeability of Myfortic and Cellcept, as the Myfortic prescribing information was not consistent with the summary of product characteristics (SPC). Section 4.4 of the Myfortic SPC, Special warnings and precautions for use, stated '[Myfortic] and [Cellcept] should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles'. By comparison, the relevant statement in the prescribing information read: 'Due to different pharmacokinetic profiles care should be taken when interchanging or substituting [Myfortic] and [Cellcept]'.

Roche submitted that the intention of the SPC was that Myfortic should not be interchanged or substituted indiscriminately with Cellcept without a good clinical reason for so doing. The prescribing information however, implied that it was acceptable to interchange the two products as long as care was taken. Roche considered that the impact of the SPC statement had been changed unnecessarily in the prescribing information, in breach of Clause 4.1 supplementary information and Clause 4.2 of the Code.

RESPONSE

Novartis noted that the issue was that the Myfortic SPC stated '[Myfortic] and [Cellcept] should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles' whereas the prescribing information read 'Due to different pharmacokinetic profiles care should be taken when interchanging or substituting [Myfortic] and [Cellcept]'.

Novartis noted that 'indiscriminate' was defined as: 'showing lack of care' (Collins English dictionary); 'chosen at random' (Chambers English dictionary) and 'making no distinctions' (Concise Oxford dictionary). In addition, Roget's Thesaurus provided random, careless, and casual as synonyms for indiscriminate. By these definitions, 'care should be taken' appeared to convey the same meaning as 'should not be indiscriminately …'.

Novartis noted that under 'Dosage and Administration', the prescribing information stated that 'Treatment should be initiated and maintained by appropriately qualified transplant specialists'. Due to the critical nature of this speciality, prescribers would be expected to be aware of the possible implications of pharmacokinetic differences between immunosuppressants. The prescribing information wording 'care should be taken' was immediately followed by the key qualifier 'due to different pharmacokinetic profiles' and thus clearly indicated the reason why the prescriber was being asked to take care. This context provided additional justification for considering that it was appropriate to ask specialist prescribers to take an appropriate degree of care rather than reproduce the SPC wording which implied, in a more negative way, that having drawn their attention to pharmacokinetic differences between products, they might still take a careless or wanton approach to conversion or substitution of the agents.

Novartis stated that it was accepted that the SPC caution against a careless approach to switching was a sensible safety measure given that current clinical experience with Myfortic was limited.

One of the two pivotal Myfortic trials (Budde *et al* 2004) specifically examined the safety and efficacy of conversion to Myfortic. Although the trial population was selected in some respects versus the general population, the trial did not support the view that additional warnings, above and beyond the recommendation to take appropriate care because of pharmacokinetic differences, were necessary for the prescriber. In this trial, 222 stable transplant patients taking the licenced dose of Cellcept underwent either conversion to Myfortic (n=159) or continuation with Cellcept (n=163) in a randomised, double-blind study design, without therapeutic drug monitoring. In this rigorous trial assessment, conversion to Myfortic was associated with no detrimental impact on either safety or efficacy at one year despite blinding of clinicians as to the identity of the agent patients were randomised to.

The apparent lack of clinical impact of the different pharmacokinetic profiles in the pivotal conversion trial might appear inconsistent with the emphasis placed on pharmacokinetic differences in the SPC. The trial findings might be explained by the fact that mycophenolic acid (MPA) exposure (AUC) was the most therapeutically relevant pharmacokinetic parameter for this class of agents, and this had been shown to be equivalent for Myfortic and Cellcept, despite the differences in bioavailability and T_{max} listed in the SPC. Novartis therefore considered that the currently available clinical conversion data which underpinned the Myfortic SPC, provided further reassurance that the prescribing information did not require amendment in order to protect patient safety as suggested by Roche.

In summary Novartis noted that Clause 4.2 of the Code stated that prescribing information consisted of, *inter alia*, 'a succinct statement of the side effects, precautions … giving, in an abbreviated form, the substance of the relevant information in the summary of product characteristics'. For the reasons outlined, Novartis considered that 'care should be taken when …' was an acceptable abbreviation and accurately conveyed the same information as 'should not be indiscriminately …'.

PANEL RULING

The Panel noted that Clause 4.2 of the Code listed the component parts of the prescribing information. One component of prescribing information was 'a succinct statement of the side-effects, precautions and contra-indications relevant to the indications in the advertisement, giving, in an abbreviated form, the substance of the relevant information in the summary of product characteristics'. Clause 4.1 stated that the information listed in Clause 4.2 must be provided. Failure to do so would therefore be a breach of Clause 4.1 and not of Clause 4.2.

The Panel noted that the statement in the Myfortic SPC that '[Myfortic] and [Cellcept] should not be indiscriminately interchanged or substituted …' referred to patients being switched from Myfortic to Cellcept and *vice versa*. The Panel noted Novartis' submission that Budde *et al* had shown that switching patients from Cellcept to Myfortic was not associated with any detrimental effects with regard to safety and efficacy. The Panel had not been provided with a copy of Budde *et al* and no data had been supplied about the conversion of patients from Myfortic to Cellcept.

The Panel noted that an SPC represented the agreed information about a medicine. The Panel considered that there was a material difference between the statement in the Myfortic SPC that '[Myfortic] and [Cellcept] should not be indiscriminately interchanged or substituted …' and the comparable statement in the prescribing information that 'care should be taken when interchanging or substituting [Myfortic] and [Cellcept]'. In the Panel's view 'indiscriminately' referred to the grounds for changing a patient from one product to the other and implied that such a switch should not be made without good clinical reason. The Panel considered that the statement in the prescribing information did not tell doctors of the caution that they must exercise in making the initial decision to swap patients from one product to the other. In the Panel's view 'Care should be taken …' referred to the manner in which patients were switched once the decision to switch had been made. The Panel thus considered that the statement in the prescribing information did not reflect the substance of the relevant information in the SPC as required by Clause 4.2. The Panel therefore ruled a breach of Clause 4.1 of the Code.

APPEAL BY NOVARTIS

Novartis submitted that the Panel ruling illustrated that the phrase 'should not be indiscriminately interchanged' was open to a number of interpretations, it was therefore important to cover four main areas: the clinical evidence that underpinned the Myfortic marketing authorization; the regulatory context from which this precautionary SPC wording arose; the interpretation of three transplant opinion leaders as to how the meaning of the prescribing information compared with that of the

SPC and specific response to the views expressed by the Panel in its decision.

Clinical evidence

Pharmacokinetics: Novartis noted that AUC of MPA was generally accepted as the most relevant pharmacokinetic parameter for efficacy and safety. Due to complexities in measuring AUC in clinical practice, measurement of the 12 hour trough level (C_0) was sometimes used as a surrogate marker for AUC.

When comparing equimolar doses of Myfortic and Cellcept, the exposure to MPA, as measured by AUC, was equivalent. In a double blinded pharmacokinetic study in 14 stable renal transplant patients, equimolar doses of Cellcept and Myfortic resulted in similar MPA AUC (Myfortic: 56μg.h/mL vs Cellcept: 55.7μg.h/mL; Budde *et al* 2002).

As a result of the enteric coating of Myfortic, MPA was released somewhat later, in the small intestine. Consequently, there was a delayed time to drug absorption (T_{lag}) and delayed time to maximum plasma concentration (T_{max}) with peak plasma concentration (C_{max}) 5-10% lower compared to Cellcept.

Because it was released in the small intestine, Myfortic might be prone to the effects of delayed gastric emptying following an evening dose, occasionally resulting in a higher variability of the trough concentration collected in the morning.

Thus the pharmacokinetic differences between MPA formulations related to the timing of dissolution of the enteric coating of Myfortic, whereas overall exposure to MPA delivered by Myfortic was equivalent to that delivered by Cellcept, an immediate release preparation.

Clinical conversion study: Novartis noted that there was no evidence to suggest a clinical safety risk in switching patients currently on Cellcept to Myfortic. This was demonstrated by Budde *et al* in which maintenance renal transplant patients, at least 6 months post-transplant were randomised either to continue on Cellcept 1g twice daily (n=163) or convert to Myfortic 720mg twice daily (n=159) over a period of 12 months. Results at three months post-conversion showed that there was no difference between Myfortic and Cellcept groups in the incidence of the most common MPA related adverse events; namely neutropenia and gastrointestinal adverse events. At 12 months post-conversion, a significant reduction in the incidence of serious infections was seen in the Myfortic group (8.8% vs 16% $p<0.05$), with no other safety differences noted. There was numerically less efficacy failure in the Myfortic vs Cellcept group (2.5% vs 6.1%) at the end of the study period. Although the difference in composite endpoint was not statistically significant, the fact that the individual efficacy parameters were each in favour of Myfortic provided additional reassurance that whatever pharmacokinetic differences existed, they did not appear to impact the efficacy of Myfortic vs Cellcept.

In summary, Novartis submitted that despite the known differences in pharmacokinetic profiles, double-blind conversion of stable patients from Cellcept to Myfortic at a minimum of 6 months from transplant was associated with no safety concerns compared to remaining on Cellcept for the duration of the study period.

Regulatory context

Novartis submitted that comments received from concerned member states in the mutual recognition procedure for Myfortic provided important context. The UK, Denmark and Spain raised the issue that although Myfortic and Cellcept both contained mycophenolic acid (MPA), they exhibited different pharmacokinetic profiles. There were concerns that prescribers considering the two products as generics could switch between them on a frequent, random basis. Hence, the following statement was suggested by Novartis and accepted by the concerned member states: '[Myfortic] and [Cellcept] should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles'.

The interpretation of transplant opinion leaders

Novartis provided three letters from key opinion leaders each supporting the company's position with regard to the wording in the prescribing information compared to that in the SPC.

Specific response to the views expressed by the Panel in its decision

Novartis noted that the Panel had stated that 'indiscriminately' referred to the grounds for changing a patient from one product to another and implied that such a switch should not be made without good clinical reason'.

Novartis submitted that the Panel had not interpreted the SPC wording correctly. The use of the wording '[Myfortic] and [Cellcept] should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles' was inserted to discourage prescribers from considering that the two products were interchangeable on a random or frequent basis. It was not intended to specifically advocate that a physician needed a clinical reason before switching from Cellcept to Myfortic, rather that physicians should be aware that because these products were not identical, clinically relevant differences in the pharmacokinetics of MPA absorption might occur. In this respect, it was clear that both the SPC and prescribing information stressed that any switching of the products should occur under careful clinical supervision.

Novartis submitted that had the Panel been given a copy of Budde *et al* to review in detail, it was possible that it would have taken a different view of the meaning of 'indiscriminately' in the SPC. In this study, clinicians were unaware of which MPA formulation patients were being allocated to, and as allocation was random, it was by definition not according to 'clinical reason'. Despite these artificially stringent study requirements, no adverse safety outcomes were noted. Indeed, converting patients to Myfortic resulted in an apparent improvement in overall safety, demonstrated by a significant decrease

in serious infections in the Myfortic group, one of the more important clinical concerns in patients receiving immunosuppressive therapy.

Novartis submitted that the lack of safety concerns demonstrated in the pivotal study had not detracted from the need to advocate caution in both the SPC and the prescribing information. Novartis considered that clinicians needed to be aware of the potential implications of differences in C_{max} and T_{max} when used in routine clinical practice, rather than in the clinical trial setting. The limitations of the study were that only conversion in one direction was investigated ie Cellcept to Myfortic, and that conversion was between full doses, in stable patients a minimum of six months from transplant. This did not cover the wide range of scenarios in which conversion (in either direction) might occur and in which the pharmacokinetic differences between the products might prove clinically relevant. Although this was currently a hypothetical concern, it was appropriate for the SPC and prescribing information to advocate care when substituting or interchanging between the agents. Novartis noted that one of the key opinion leaders from whom it had sought an opinion, considered that both the SPC and the prescribing information responsibly highlighted the need to be aware of pharmacokinetic differences between the two products particularly as only conversion from Cellcept to Myfortic was addressed.

Novartis noted that 'The Panel considered the statement in the prescribing information did not tell doctors of the caution that they must exercise in making the initial decision to swap patients from one product to the other'. Novartis submitted that the prescribing information clearly stated that treatment should be initiated and maintained by appropriately qualified transplant specialists who would be aware of the implications of switching immunosuppressive medicines with different pharmacokinetic profiles. Novartis had requested an expert opinion on this point and had been told that 'Immunosuppressive drugs are managed by transplant specialists and not by general practitioners and therefore changes in doses or switching medication are usually made on good clinical grounds and with care to avoid rejection and or drug toxicity'.

Novartis submitted that by stating in the prescribing information that 'care should be taken' in conjunction with the key qualifier 'due to pharmacokinetic differences', it had highlighted that clinicians should be aware of differences between the two products not only in making a clinical decision to switch but also during the process of switching itself. Further advice from a key opinion leader was that 'care should be taken' strengthened and went further than the wording in the SPC by emphasising the need for care to be taken in monitoring the results if switching.

Novartis submitted that the intent of the wording in the SPC and the prescribing information was to make prescribers aware that Myfortic and Cellcept were not identical and ensure that appropriate care was taken when converting between them. Even though equivalent exposure (AUC) at licenced doses had been established for the two MPA formulations, and this was accepted to be the most therapeutically relevant parameter, a cautionary statement was appropriate in view of the C_{max} and T_{max} differences in order to discourage random, or frequent switching in clinical practice (eg pharmacy substitution) as if Myfortic were a generic product. That the prescribing information achieved the intended meaning of the SPC in these respects was confirmed by the three key opinion leader submissions provided.

Summary

Novartis submitted that taking into consideration the following:

- Standard dictionary definitions of indiscriminate included 'showing lack of care', 'chosen at random' and 'making no distinctions'.
- The word 'care' went further than the SPC in highlighting the need for careful clinical supervision in switching between products.
- No safety concerns had been demonstrated in the clinical conversion of Cellcept to Myfortic.
- Although differences in C_{max} and T_{max} had been shown in pharmacokinetic studies, the possible clinical risks of frequent 'indiscriminate' or random conversion between MPA formulations remained hypothetical. In the interests of safety, if converting, care, rather than clinical justification (as has been interpreted by the Panel) was required.
- The appropriately qualified transplant prescriber understood the possible clinical implications of different pharmacokinetic profiles.
- Three key opinion leaders had confirmed that the prescribing information conveyed the same meaning as the SPC.

Novartis submitted that the statement in the prescribing information 'Due to different pharmacokinetic profiles care should be taken when interchanging or substituting mycophenolate sodium and mycophenolate mofetil' was a true reflection of the data and the intended meaning of the SPC and thus was not in breach of the Code.

COMMENTS FROM ROCHE

Roche noted that the supplementary information to Clause 4.1 of the Code stated that 'The prescribing information must be consistent with the summary of product characteristics for the medicine'. Hence, although Novartis had gone to great lengths to explain the intent of the wording of the Myfortic prescribing information, Roche considered that it was only on the SPC wording *per se* that the case should be judged.

Roche noted that the regulatory authorities had clearly required that it be stipulated in Section 4.4 of the Myfortic SPC, Special warnings and precautions for use, that '[Myfortic] and [Cellcept] should not be indiscriminately interchanged or substituted because of their different pharmacokinetic profiles'. Roche alleged that failure to follow this requirement could potentially compromise efficacy and patient safety,

through not only lack of efficacy but also toxicity. The importance of patient selection cited in the SPC was not reflected in the softer Myfortic prescribing information ('care should be taken ...').

Roche stated that when comparing Section 5.2 Pharmacokinetic properties of the respective SPCs, the following differences existed between Cellcept and Myfortic:

- Myfortic had a T_{max} of 1.5-2 hours, compared to 30-60 minutes for Cellcept.
- When Myfortic was taken with a high fat meal, there was no effect on MPA AUC. However, 'T_{lag} and T_{max} were on average 3-5 hours delayed, with several patients having a T_{max} of >15 hours. The effect of food on Myfortic might lead to an absorption overlap from one dose interval to another'.

This effect of food on MPA pharmacokinetics resulted in the recommendation in Section 4.2 Posology and method of administration, that 'Myfortic can be taken with or without food. Patients may select either option but must adhere to their selected option'.

Apart from a decreased C_{max} , there were no differences in Cellcept pharmacokinetics or exposure when given with food, and no specific recommendations with regard to dosing and food intake.

Roche alleged that a further example of pharmacokinetic differences was detailed in Novartis' appeal, highlighting diurnal variation in trough concentrations of Myfortic, which once again was not evident with Cellcept. Given the magnitude of the variability of some of the pharmacokinetic parameters, the potential impact on individual patients of switching medicines resulted in the statement in the SPC that Cellcept and Myfortic 'should not be indiscriminately interchanged or substituted'.

Roche noted that the supplementary information to Clause 4.1 of the Code stated that 'Each promotional item for a medicine must be able to stand alone'. Roche alleged that Novartis' argument was not immediately accessible to the reader of the prescribing information and the impression left about 'care' was both lightweight and misleading.

Roche alleged that given the potential impact of this precaution on safe prescribing, it was unclear as to why Novartis had not used the verbatim wording of the original. Although the Code stated that the prescribing information should consist of a 'succinct statement of the side-effects, precautions and contra-indications', the difference between the original SPC precaution and the statement as it appeared in the prescribing information was only 14 characters (including spaces), as the word count was identical.

Roche alleged that this prescribing information was complicit with other materials produced by Novartis which used softer wording to imply the safety of switching, thereby demonstrating Novartis' general position on this matter. Roche stated that whilst it was not the subject of a formal complaint as yet, it drew attention to two examples of how the wrong impression might be given to prescribers of the safety of switching, without qualifying the relevant SPC precaution. These being a Novartis Media Release, dated 13 September 2004, which stated 'Studies have shown that patients currently on [Cellcept] can be safely converted to Myfortic without compromising efficacy or tolerability' and a Pharmafocus article, October 2004, which stated 'Novartis says studies show that patients being treated with Cellcept can be safely converted to Myfortic without compromising safety or efficacy'.

Roche therefore agreed with the Panel that 'the statement in the prescribing information did not reflect the substance of the relevant information in the SPC…' breached Clause 4.1.

APPEAL BOARD RULING

The Appeal Board noted that the statement in the Myfortic SPC that '[Myfortic] and [Cellcept] should not be indiscriminately interchanged or substituted …' referred to patients being switched from Myfortic to Cellcept and *vice versa*. Budde *et al* had only shown that switching patients from Cellcept to Myfortic was not associated with any detrimental effects with regard to safety and efficacy.

The Appeal Board noted that the statement in the Myfortic SPC that '[Myfortic] and [Cellcept] should not be indiscriminately interchanged or substituted' was suggested by Novartis and agreed by the regulatory authorities. The Appeal Board considered the statement was slightly unusual in its use of the word 'indiscriminately'. The relevant statement in the prescribing information referred to the need to take care. The Appeal Board also noted that the statement in the prescribing information read 'care should be taken **when** interchanging or substituting [Myfortic] and [Cellcept]' (emphasis added). In the Appeal Board's view 'when' in that statement meant that interchanging or substituting the two products was acceptable provided it was done with care, whereas the SPC statement implied that prescribers should be cautious about making the decision to change therapy at all.

The Appeal Board considered that there was an important difference between the two statements such that the statement in the prescribing information did not reflect the substance of the relevant information in the SPC as required by Clause 4.2 of the Code. The Appeal Board upheld the Panel's ruling of a breach of Clause 4.1. The appeal was unsuccessful.

Complaint received **12 October 2004**

Case completed **26 January 2005**

CASE AUTH/1645/10/04

PFIZER CONSUMER HEALTHCARE v GLAXOSMITHKLINE CONSUMER HEALTHCARE

NiQuitin CQ Clinical Guide

Pfizer Consumer Healthcare complained about a NiQuitin CQ Clinical Guide issued by GlaxoSmithKline Consumer Healthcare which was used as a leavepiece for nurses, smoking cessation advisers and the occasional general practitioner. The NiQuitin CQ range of nicotine replacement therapy (NRT) for relief of nicotine withdrawal symptoms during smoking cessation included 24-hour patches. Pfizer marketed the Nicorette range of 16-hour NRT patches.

The claim 'NiQuitin CQ 21mg patch offers the confidence of 24-hour craving protection' appeared at the top of a page above a schematic visual which showed the difference between NiQuitin 24-hour patch (continuous wear from one day to the next) and a 16-hour patch (intermittent wear from one day to the next). The visual showed a continuous arrow for NiQuitin 24-hour and an intermittent arrow for the 16-hour patch. The x axis was labelled 'time' with no further description.

Pfizer Consumer Healthcare alleged that the claim was inconsistent with the visual which showed the dosing schedule for 24- and 16-hour NRT patches and not craving protection. The visual was alleged to be misleading. Furthermore, in the context of its title, relating to craving protection, the visual misled the reader into believing that the 24-hour patch provided total and constant, 'round the clock' craving control, whereas the 16-hour patch provided inconsistent and abruptly broken craving control. The visual implied that the 16-hour patch was an inferior form of NRT when compared with the 24-hour patch due to a complete lack of craving control for 8 hours of the day. At best the visual oversimplified craving control; cravings would not return suddenly and absolutely upon removal of the 16-hour patch as suggested.

Although it was not clear from the visual, as the x axis (time) was not labelled with hours of the day, the breaks between the arrows were presumably designed to denote night-time periods where the 16-hour patch would be removed. Nonetheless, the visual was still misleading as it implied that craving control was needed overnight which was not so; sleeping patients would not experience cravings.

In response to Pfizer Consumer Healthcare's concerns GlaxoSmithKline Consumer Healthcare had argued that the title related to the entire page and not the visual. Pfizer Consumer Healthcare stated that the size and emphasis of the font used was identical to that of a heading to a graph further down the page and on other pages throughout the guide. It would not be clear to health professionals that this was intended to be a page title. The visual was misleading in the context of the heading which related to craving protection and not dosing schedule as depicted in the visual. Pfizer Consumer Healthcare alleged that the claim and visual were misleading.

The Panel considered that the claim 'NiQuitin CQ 21mg offers the confidence of 24-hour craving protection' would not be read as the page heading. The chapter heading on the facing page (page 8) was in a slightly higher position, larger font size and different colour to the claim at issue which, in the Panel's view, might be read as a subheading to the section which started with the visual.

The Panel considered that it was misleading to place the visual which purported to show the dosage schedule immediately beneath the claim which referred to craving protection. Readers would assume that the visual related to craving protection and that was not so. The material was misleading in this regard. The Panel ruled breaches of the Code. The Panel considered that the bold continuous line for NiQuitin CQ and the broken line for the 16-hour patch implied, in light of the claim at issue, that NiQuitin CQ gave continuous craving protection and the 16-hour patch gave intermittent craving protection and was inferior in this regard. This impression was compounded by the word 'confidence' in the claim at issue which in conjunction with the visual implied a benefit not attributable to the 16-hour patch. The descriptions 'Continuous wear from 1 day to the next' and 'Intermittent wear from 1 day to the next' which appeared beneath 'NiQuitin CQ 24-hour patch' and '16-hour patch' respectively were in such a small type face that they did not negate the immediate visual impression given by the material. The Panel considered that the visual oversimplified the differences in craving control between the products and was misleading in this regard. Breaches of the Code were ruled. The Panel did not consider that the material implied that craving control was needed when patients were asleep. No breach was ruled on this point.

The claim 'NiQuitin CQ patches provide constant, 24-hour nicotine replacement with steady-state nicotine plasma levels being achieved after the 2nd day of treatment. This 24-hour administration of nicotine means that patients get the benefit of craving relief all day, with trials confirming that NiQuitin CQ 24-hour patches significantly reduce cravings in the morning and throughout the entire day' appeared on page 9 of the Clinical Guide immediately below the visual referred to above. Pfizer Consumer Healthcare noted that the summary of product characteristics (SPC) was cited in support of the claim that NiQuitin provided constant amounts of nicotine over a 24-hour period. In the context of a discussion of pharmacokinetics the word 'constant' could only be taken to mean fixed and invariable. However, plasma levels for the 24 hour patch fluctuated over a 24-hour period and the SPC confirmed that plasma levels were indeed only 'relatively constant'. Pfizer Consumer Healthcare

alleged that the text was exaggerated and misleading.

The Panel did not consider that the claim that NiQuitin CQ patches would 'provide constant, 24-hour nicotine replacement' would be read as referring to constant nicotine plasma levels as alleged. Whilst the second phrase of the sentence read 'with steady-state nicotine plasma levels being achieved after the 2nd day of treatment', the Panel considered that the construction of the sentence was such that it was sufficiently clear that the provision of 'constant 24-hour nicotine.' referred to the provision of a constant supply of nicotine for 24 hours. No breach of the Code was ruled.

Pfizer Consumer Healthcare stated that the use of the phrase 'This 24-hour administration' in the context of a page comparing craving protection with a 16- and 24-hour patch implied that only 24-hour administration could provide craving relief all day. Clearly 'all day' craving relief as described in this section could only refer to waking hours as sleeping patients did not crave.

The Panel did not accept that the use of the word 'this' in the claim 'This 24-hour administration of nicotine means…' implied that only 24-hour patches provided an appropriate duration of craving relief as alleged. The claim described a feature of NiQuitin CQ. The Panel ruled no breach of the Code on this narrow point.

Pfizer Consumer Healthcare alleged that the claim 'with trials confirming that NiQuitin CQ 24-hour patches significantly reduce cravings in the morning and throughout the entire day' was a hanging comparison. It was not clear as to what the significant reduction in cravings related. As most of the page related to comparisons with the 16-hour patch it could be interpreted that the claim was intended to compare NiQuitin CQ 24-hour patch with Nicorette 16-hour patch. The referencing was inaccurate as the claim referred to 'trials' yet only one was cited (Shiffman *et al* 2000). Pfizer Consumer Healthcare was not aware of multiple trials that had compared the two patches on cravings relief.

The Panel considered that the claim that trials confirming that NiQuitin CQ '…significantly reduce cravings' was not a hanging comparison; it merely stated what the product did. The Panel noted that the claim appeared on a page comparing NiQuitin and the 16-hour patch within a section that clearly related to features of NiQuitin and did not compare the products. No breach of the Code was ruled.

The Panel noted that the claim referred to trials but only Shiffman *et al* was cited. The Panel considered that this was not unacceptable. References were only required under the Code when a published study was referred to. The reference cited was given as an example. Other data showing that NiQuitin CQ reduced cravings was available. The Panel did not consider that the citing of one reference, in association with the use of the word 'trials' when other trials were available was misleading. No breach of the Code was ruled.

The claim 'NiQuitin CQ 21 mg patch offers greater morning craving relief than a 16-hour patch for those likely to need it most' appeared on page 9 as a heading to a graph and beneath the paragraph at issue above.

Pfizer Consumer Healthcare stated that it had previously been concerned about the use of the highly selected population studied by Shiffman *et al* to support general claims relating to craving protection for NiQuitin CQ patch. This population consisted of heavily dependent smokers who prior to study entry (ie prior to smoking cessation) reported more craving for cigarettes in the morning than the rest of the day, smoked within 30 minutes of waking and who now wished to quit. This level of nicotine dependency was not representative of the general quitting population. Furthermore, smokers who experienced severe morning cravings whilst smoking did not necessarily experience the same upon quitting. It was not clear from the graph that the data was derived from a highly selected population of ex-smokers; the general impression was that the 24-hour patch provided greater craving relief for the general quitting population. The presentation of the data was alleged to be misleading.

Pfizer Consumer Healthcare alleged that the claim used in the NiQuitin CQ Clinical Guide was not sufficiently different from the claims ruled in breach of the Code in Case AUTH/1253/11/01 and therefore the continued use of the selected group of patients without proper and explicit qualification constituted a breach of undertaking. The use of the small footnote to the visual and the phrase 'in those likely to need it most' did not counter the impression given that the data was obtained from, and applied to, the more general quitting population. However, Pfizer Consumer Healthcare maintained that the use of the data in this general context was misleading.

The Panel considered that the claim and graph at issue was sufficiently different to the material at issue in Case AUTH/1253/11/01 for it not to constitute a breach of undertaking. The current material referred to Shiffman *et al* as being in 'those likely to need it most'. In the Panel's view this would be read as a reference to particular types of smokers, ie those who suffered morning cravings and not the general smoking population. No breach of the Code was ruled. Further, the Panel did not consider that the claim and graph implied that the data related to the general quitting population as alleged. No breach of the Code was ruled.

Pfizer Consumer Healthcare noted that the Clinical Guide did not include a clear date of last revision and furthermore the date contained within the code NCQ/PW/0903/005 could not relate to the date the material was last revised due to the dates cited on the prescribing information.

The Panel did not consider that use of the promotional code NCQ/PW/0903/005 was sufficient to satisfy the requirement of the Code to include the date the promotional material was drawn up or last revised. A further difficulty was that the promotional code indicated the material was drawn

up in September 2003 which was not the date of preparation given that the prescribing information was last revised in January 2004. The Panel considered that the requirements of the Code had not been met and a breach was ruled.

Pfizer Consumer Healthcare complained about a 24 page NiQuitin CQ Clinical Guide (ref NCQ/PW/0903/005) issued by GlaxoSmithKline Consumer Healthcare. The NiQuitin CQ range of nicotine replacement therapy (NRT) for relief of nicotine withdrawal symptoms during smoking cessation included 24-hour patches. Correspondence between the companies had failed to resolve the matter.

Pfizer marketed the Nicorette range of NRT which included 16-hour patches.

GlaxoSmithKline Consumer Healthcare stated that the Clinical Guide was aimed at nurses and smoking cessation advisers primarily, although an occasional GP might be interested to see it. It was used by the representatives as a leavepiece for customers to read in their own time, and was written in a style that was more akin to a magazine than a scientific journal so that it was easy for the intended audience to digest.

1 Claim 'NiQuitin CQ 21mg patch offers the confidence of 24-hour craving protection' plus visual

The claim appeared at the top of page 9 above a visual, described as 'schematic only', which showed the difference between NiQuitin 24-hour patch (continuous wear from one day to the next) and 16-hour patch (intermittent wear from one day to the next). The visual showed a continuous arrow for NiQuitin 24-hour and an intermittent arrow for the 16-hour patch. The x axis was labelled 'time' with no further description.

COMPLAINT

Pfizer Consumer Healthcare alleged that the claim 'NiQuitin CQ 21 mg patch offers the confidence of 24-hour craving protection' was inconsistent with the visual which merely showed the dosing schedule for 24- and 16-hour nicotine replacement patches and did not consider craving protection at all. The visual was alleged to be misleading as the overall impression was that it related to craving control and that was not so.

Furthermore, in the context of its title, relating to craving protection, the visual misled the reader into believing that the 24-hour patch provided total and constant, 'round the clock' craving control, whereas the 16-hour patch merely provided inconsistent and abruptly broken craving control. The impression was that the 16-hour patch was an inferior form of NRT when compared with the 24-hour patch due to a complete lack of craving control for 8 hours of the day (the visual was not drawn accurately as the 8 hour blocks were visually under-represented). At best the visual oversimplified the situation regarding craving control as cravings would not return suddenly and absolutely upon removal of the 16-hour patch as suggested.

Although it was not clear from the visual, as the x axis (time) was not labelled with hours of the day, the breaks between the arrows were presumably designed to denote night-time periods where the 16-hour patch would be removed. Nonetheless, the visual was still misleading as it created an impression that craving control was needed overnight. This was clearly not the case as patients would be asleep and hence not experiencing cravings.

In response to Pfizer Consumer Healthcare's concerns GlaxoSmithKline Consumer Healthcare had argued that the title related to the entire page and not the visual. Pfizer Consumer Healthcare stated that the size and emphasis of the font used was identical to that of a heading to a graph further down the page and on other pages throughout the guide. Pfizer Consumer Healthcare did not consider that it would be clear to health professionals that this was intended to be a page title.

GlaxoSmithKline Consumer Healthcare seemed to have missed the point which was that the visual was misleading in the context of the heading which related to craving protection and not dosing schedule as depicted in the visual.

It was alleged that the claim and visual were misleading in breach of Clauses 7.2 and 7.8 of the Code.

RESPONSE

GlaxoSmithKline Consumer Healthcare noted that the visual at issue was preceded by the final paragraph of page 8, entitled 'Why use a 24-hour patch?' which described the rationale behind the different profiles of 16- and 24-hour patches. The paragraph stated 'If a nicotine patch is always removed at night, nicotine plasma levels fall by morning without ever reaching a steady state. The application of a new patch every morning therefore means that nicotine administration effectively starts from scratch every day and leaves the patient susceptible to morning cravings'. Pfizer Consumer Healthcare had made no complaint in this regard and the visual that it complained about was simply a diagrammatic representation of this. The headline 'NiQuitin CQ 21mg patch offers the confidence of 24-hour craving protection' not only related to the visual but also the text beneath it.

The visual was clearly labelled as a schematic representation and the arrows labelled 'continuous wear' or 'intermittent wear'. In an effort to be fair to its competitors, GlaxoSmithKline Consumer Healthcare deliberately made the gaps slightly smaller between the arrows on the 16-hour patch, to allow for absorption from the skin depot after removal of the 16-hour patch at night, but not so small that it would negate Pfizer Consumer Healthcare's 'lack of nicotine delivery overnight' promotional platform. There was no mention of craving control or protection on the visual and the text underneath made the link between 24-hour wear and craving relief, 24-hour craving protection was a feature of NiQuitin CQ patch and it was entirely valid for GlaxoSmithKline Consumer Healthcare to draw attention to this. Cravings could strike at any time, including during the night when a minority of smokers woke up to feed their addiction.

Those with abnormal shift patterns might also particularly benefit from 24-hour craving protection so that no matter what time of day or night it was, using a 24-hour patch would give them protection. However, the key benefit of 24-hour protection was the fact that better morning craving control was achieved with 24-hour wear. The NiQuitin CQ 21mg patch summary of product characteristics (SPC) made it clear that 'use for 24-hours is recommended to optimise the effect against morning cravings'.

GlaxoSmithKline Consumer Healthcare considered the heading and the visual were not misleading and did not contravene Clauses 7.2 and 7.8.

PANEL RULING

The Panel considered that the claim 'NiQuitin CQ 21mg offers the confidence of 24-hour craving protection' would not be read as the page heading. The facing page (page 8) was headed 'Chapter 2: NiQuitin CQ 21mg Patch'. The heading was in a slightly higher position, larger font size and different colour to the claim at issue which, in the Panel's view, might be read as a subheading to the section which started with the visual.

The Panel considered that it was misleading to place the visual which purported to show the dosage schedule immediately beneath the claim which referred to craving protection. A reader would assume that the visual related to craving protection and that was not so. The material was misleading in this regard. The Panel ruled breaches of Clauses 7.2 and 7.8 of the Code.

The Panel considered that the bold continuous line for NiQuitin CQ and the broken line for the 16-hour patch implied, in light of the claim at issue, that NiQuitin CQ gave continuous craving protection and the 16-hour patch gave intermittent craving protection and was inferior in this regard. This impression was compounded by the word 'confidence' in the claim at issue which in conjunction with the visual implied a benefit not attributable to the 16-hour patch. The descriptions 'Continuous wear from 1 day to the next' and 'Intermittent wear from 1 day to the next' which appeared beneath 'NiQuitin CQ 24-hour patch' and '16-hour patch' respectively were in such a small type face that they did not negate the immediate visual impression given by the material. The Panel considered that the visual oversimplified the differences in craving control between the products and was misleading in this regard. Breaches of Clauses 7.2 and 7.8 were ruled.

The Panel did not consider that the material implied that craving control was needed when patients were asleep, as alleged. No breach of Clauses 7.2 and 7.8 was ruled on this point.

2 Claim 'NiQuitin CQ patches provide constant, 24-hour nicotine replacement with steady-state nicotine plasma levels being achieved after the 2nd day of treatment. This 24-hour administration of nicotine means that patients get the benefit of craving relief all day, with trials confirming that NiQuitin CQ 24-hour patches significantly reduce cravings in the morning and throughout the entire day'

The claim appeared on page 9 of the Clinical Guide immediately below the visual referred to in point 1 above.

COMPLAINT

Pfizer Consumer Healthcare stated that the SPC was provided as a reference to NiQuitin providing constant amounts of nicotine over a 24-hour period. Section 5.2 of the SPC stated:

> 'Following transdermal application, the skin rapidly absorbs nicotine released initially from the patch adhesive. The plasma concentrations of nicotine reach a plateau within 2-4 hours after initial application of NiQuitin CQ Clear with relatively constant plasma concentrations persisting for 24 hours or until the patch is removed. Approximately 68% of the nicotine released from the patch enters systemic circulation and the remainder of the released nicotine is lost via vaporisation from the edge of the patch.
>
> With continuous daily application of NiQuitin CQ Clear (worn for 24 hours), dose-dependent steady state plasma nicotine concentrations are achieved following the second NiQuitin CQ Clear application and are maintained throughout the day. These steady state maximum concentrations are approximately 30% higher than those following a single application of NiQuitin CQ Clear.'

In the context of a discussion of pharmacokinetics the word 'constant' could only be taken to mean fixed and invariable. However, plasma levels for the 24-hour patch fluctuated over a 24-hour period and the SPC confirmed that plasma levels were indeed only 'relatively constant'.

GlaxoSmithKline Consumer Healthcare's view was that the text at issue stated that NiQuitin CQ patches provided constant 24-hour nicotine replacement, not that constant amounts of nicotine over a 24-hour period were provided and that the Clinical Guide was not a pharmacokinetic journal, but a simple guide for health professionals.

Nevertheless Pfizer Consumer Healthcare maintained that the sentence related to pharmacokinetics and therefore the word constant would be construed as being related to plasma levels. Furthermore, if GlaxoSmithKline Consumer Healthcare had intended the word 'constant' to relate to 24-hour usage then why use the tautology '….constant, 24-hour…'? The fact that the clinical guide was not a pharmacokinetic journal was of no relevance as pharmacokinetics might be discussed in a variety of publications including promotional material.

It was alleged that the text was exaggerated and misleading in breach of Clause 7.2 of the Code.

The use of the phrase 'this 24-hour administration' in the context of a page comparing craving protection with 16- and 24-hour patch implied that only 24-hour administration could provide craving relief all day. Clearly 'all day' craving relief as described in this

section could only refer to waking hours as patients did not crave whilst they slept.

Shiffman *et al* (2000) cited in the Clinical Guide compared the 16-hour patch with the 24-hour patch on 'all day' cravings and demonstrated superiority for the latter on this parameter. However Shiffman *et al* did not include a placebo arm for either 'morning' or 'all day' comparisons and therefore could not show that 16-hour patch had no effect on 'all day' cravings. Also, the discussion section stated: 'The demonstrated superiority of the 21-mg/24-hour dosing regimen over 15 mg/16-hour should not be taken as evidence the latter is ineffective against craving and withdrawal. This study did not include a placebo group against which the 15 mg/16-hour patch's absolute efficacy could be evaluated, but published data show that the 15 mg/16-hour patch is superior to placebo for the relief of craving and withdrawal, and for smoking cessation'.

In correspondence GlaxoSmithKline Consumer Healthcare had agreed that Shiffman *et al* should not be taken to mean that the 16-hour patch did not work. However, it did not address Pfizer Consumer Healthcare's concerns that use of the word 'this' in the context of a comparative page implied that 'only' 24 hour administration could provide relief all day.

It was alleged that the claim was misleading in breach of Clause 7.2 of the Code.

The claim 'with trials confirming that NiQuitin CQ 24-hour patches significantly reduce cravings in the morning and throughout the entire day' constituted a hanging comparison as it was not clear as to what the significant reduction in cravings related. As most of the page related to comparisons with the 16-hour patch it could be interpreted that the claim was intended to compare NiQuitin CQ 24-hour patch with Nicorette 16-hour patch. The referencing was inaccurate as the claim referred to 'trials' yet only one was cited (Shiffman *et al*). Pfizer Consumer Healthcare was not aware of multiple trials that had compared the two patches on cravings relief.

A breach of Clause 7.2 of the Code was alleged.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated the text did not state that 'NiQuitin CQ provides constant amounts of nicotine over a 24-hour period' as alleged. It stated 'NiQuitin CQ patches provide constant, 24-hour nicotine replacement,' as in a continuous/persistent supply for 24 hours as opposed to 16 hours. Being immediately underneath the dosing schedule diagram reinforced this simple message of continuous delivery versus intermittent delivery, making the meaning clear to the nurse readership. However, it also held true in the pharmacokinetic context, where plasma concentrations were relatively constant once the plateau had been reached. The SPC stated there were 'relatively constant plasma concentrations persisting for 24 hours or until the patch is removed'. In a previous case, AUTH/1253/11/01, there was no complaint about the use of the word constant in a similar context in one of the claims at issue; 'constant 24 hour nicotine replacement' as it was clear in both cases what was intended to be conveyed.

GlaxoSmithKline Consumer Healthcare submitted there was no breach of Clause 7.2 of the Code.

Even if the word 'this' was removed from the claim, 'This 24-hour administration of nicotine means that patients get the benefit of craving relief all day, with trials confirming that NiQuitin CQ 24-hour patches significantly reduce cravings in the morning and throughout the entire day', the meaning of the sentence would be the same. The claim was not '**Only** 24-hour administration of nicotine means that…..'. The SPC made it clear that morning craving relief was optimised by 24-hour wear, 'use for 24 hours is recommended to optimise the effect against morning cravings'. Taking the patch off at night and therefore not having 24-hour administration would leave a gap in this protection. It was not unreasonable for GlaxoSmithKline Consumer Healthcare to draw attention to its own product's benefits (in this case craving relief) without also stating that a competitor might also have some efficacy. GlaxoSmithKline Consumer Healthcare submitted there was no breach of Clause 7.2.

GlaxoSmithKline Consumer Healthcare submitted that 'significantly reduce' was not a hanging comparative, but a statement of efficacy consistent with the marketing authorization. Had it said 'reduces significantly more cravings', 'significantly reduce cravings faster' or something similar, then GlaxoSmithKline would have needed to qualify that with which it was being compared. GlaxoSmithKline Consumer Healthcare denied a breach of Clause 7.2.

The reference cited was an example of the efficacy compared to Nicorette patch, an established and effective treatment. Showing significantly increased efficacy compared to an established active comparator made efficacy versus placebo implicit. The statement referred to 'trials' as there were a number of trials showing that NiQuitin CQ significantly reduced cravings. The requirement in the Code to provide a reference was when material referred to published studies. In this case, GlaxoSmithKline Consumer Healthcare cited the only head-to-head comparison with Nicorette patch, and used section 5.1 of the SPC rather than other published studies to support the efficacy shown in trials versus placebo ('The severity of cravings was reduced by at least 35% at all times of day during the first two weeks of abstinence, compared to placebo ($p<0.05$)').

PANEL RULING

The Panel did not consider that the claim that NiQuitin CQ patches would 'provide constant, 24-hour nicotine replacement' would be read as referring to constant nicotine plasma levels as alleged. Whilst the second phrase of the sentence read 'with steady-state nicotine plasma levels being achieved after the 2nd day of treatment', the Panel considered that the construction of the sentence was such that it was sufficiently clear that the provision of 'constant 24-hour nicotine.' referred to the provision of a constant supply of nicotine for 24 hours. The Panel ruled no breach of Clause 7.2 of the Code in this regard.

The Panel did not accept that the use of the word 'this' in the claim 'This 24-hour administration of nicotine means…' implied that only 24-hour patches provided an appropriate duration of craving relief as alleged. The claim described a feature of NiQuitin CQ. The Panel ruled no breach of Clause 7.2 of the Code on this narrow point.

The Panel considered that the claim that trials confirming that NiQuitin CQ '…significantly reduce cravings' was not a hanging comparison. It was merely a statement of what the product did. The Panel noted that the claim appeared on a page comparing NiQuitin and the 16-hour patch within a section that clearly related to features of NiQuitin and did not compare the products. Thus the Panel ruled no breach of Clause 7.2 of the Code.

The Panel noted that the claim referred to trials but only one reference, Shiffman *et al*, was given. The Panel considered that this was not unacceptable. References were only required under the Code when a published study was referred to. The reference cited was given as an example. Other data showing that NiQuitin CQ reduced cravings was available. The Panel did not consider that the citing of one reference, in association with the use of the word 'trials' when other trials were available, was misleading. No breach of Clause 7.2 of the Code was ruled.

3 Claim 'NiQuitin CQ 21mg patch offers greater morning craving relief than a 16-hour patch for those likely to need it most'

The claim appeared on page 9 as a heading to a graph and beneath the paragraph at issue at point 2 above.

COMPLAINT

Pfizer Consumer Healthcare stated that it had previously been concerned about the use of the highly selected population studied by Shiffman *et al* to support general claims relating to craving protection for NiQuitin CQ patch. This population consisted of heavily dependent smokers who prior to study entry (ie prior to smoking cessation) reported more craving for cigarettes in the morning than the rest of the day, smoked within 30 minutes of waking and who now wished to quit. Clearly there were many 'types' of smokers and this level of nicotine dependency was not representative of the general quitting population. Furthermore, smokers who experienced severe morning cravings whilst smoking did not necessarily experience the same upon quitting.

It was not clear from the graph that the data was derived from a highly selected population of ex-smokers and the general impression was that the 24-hour patch provided greater craving relief for the general quitting population.

GlaxoSmithKline Consumer Healthcare stated in correspondence that of the general smoking population who wanted to participate in clinical trials of smoking cessation, 62% fulfilled the criteria of Shiffman *et al*. However, Pfizer Consumer Healthcare did not believe that smokers wanting to be involved in clinical trials were necessarily representative of the general smoking population and even if one accepted that they might be, there were still 38% of the population who did not meet the Shiffman *et al* criteria.

It was alleged that presentation of this data in this manner was misleading and in breach of Clause 7.2 of the Code.

Of particular concern was that in Case AUTH/1253/11/01 the Panel had considered that the claims

'NiQuitin CQ patches have the advantage of offering constant 24 hour nicotine replacement, significantly reducing morning cravings' and '….compared with the Nicorette 16 hour patch, NiQuitin CQ can significantly reduce cravings both in the morning and throughout the day', based upon this same selected group of patients, were in breach of the Code.

It had previously been ruled that a reader would assume that the claims related to the general smoking population rather than a subgroup of highly dependent smokers. A footnote beneath a comparative bar chart was not considered enough to negate the impression.

Pfizer Consumer Healthcare alleged that the claim used in the NiQuitin CQ Clinical Guide was not sufficiently different from the claims ruled in breach of the Code in Case AUTH/1253/11/01 and therefore the continued use of the selected group of patients without proper and explicit qualification constituted a breach of undertaking. The use of the small footnote to the visual and the phrase 'in those likely to need it most' did not counter the impression given that the data was obtained from, and applied to, the more general quitting population.

GlaxoSmithKline Consumer Healthcare conceded that the typeface was 'probably too small' and had offered to amend it in the next print run. However, Pfizer Consumer Healthcare maintained that the use of the data in this general context was misleading in breach of Clauses 2, 7.2 and 22 of the Code.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated that the study population in Shiffman *et al* matched the characteristics of most treatment studies used as the basis for licence applications. In fact, of the general smoking population who wanted to participate in clinical trials of smoking cessation, 62% fulfilled the exact criteria of Shiffman *et al*, so it was certainly representative of a substantial proportion of the general quitting population. It was also well established that the vast majority of smokers (70%) wanted to quit. GlaxoSmithKline Consumer Health took the Panel's rulings very seriously and had no wish to mislead its audience or breach its undertakings.

The headline deliberately and obviously included the phrase 'for those likely to need it most' to highlight to readers that these were a particular type of smoker and to focus on the fact that these patients suffered morning cravings, as the benefit claimed was 'greater morning craving relief'. Previous rulings were based on a possible misinterpretation that the claim could

apply to the entire quitting population. The caveat 'in those likely to need it most' in the headline avoided that interpretation. To expand on this, the graph itself was also labelled with the exact criteria, using the same font size as all other diagram labels. In the spirit of co-operation GlaxoSmithKline Consumer Healthcare offered to increase the font size in the next print run, as it was keen to resolve these disputes between the companies rather than resorting to the Authority. GlaxoSmithKline Consumer Healthcare did not consider this visual was misleading and considered that it did not breach Clause 7.2.

GlaxoSmithKline Consumer Healthcare submitted that the clinical guide did not breach Clause 22 as the title clearly stated that the data referred to a particular subgroup of patients and the labelling immediately beneath the graph gave the exact criteria.

Clause 2 was reserved for the most severe censure. GlaxoSmithKline Consumer Healthcare took the Code very seriously and strongly disagreed with the allegation that it had brought the industry into disrepute.

PANEL RULING

The Panel noted that the claim and graph at issue was different to the material at issue in Case AUTH/1253/11/01. The current material referred to Shiffman *et al* as being in 'those likely to need it most'. In the Panel's view this would be read as a reference to particular types of smokers, ie those who suffered morning cravings and not the general smoking population.

The Panel considered that the material was not sufficiently similar to the previous material for it to constitute a breach of undertaking. No breach of Clause 22 of the Code was ruled. It thus followed that there would not be a breach of Clause 2.

The Panel did not consider that the claim and the graph implied that the data related to the general quitting population as alleged. The claim referred to patients most likely to need morning craving relief; it would thus be read as applying to a particular subpopulation. No breach of Clause 7.2 of the Code was ruled.

4 Date of Preparation

COMPLAINT

Pfizer Consumer Healthcare noted that the NiQuitin CQ Clinical Guide did not carry a date of last revision. GlaxoSmithKline Consumer Healthcare had argued that the date of preparation was integral to the unique code for the item ie NCQ/PW/0903/005. Presumably this meant that the item was prepared in September 2003, although it could also be interpreted as 9 March 2005. This would become particularly confusing to readers after this later date as there would be two potential dates of preparation/last revision contained within the unique code.

Pfizer Consumer Healthcare did not see how the data of preparation/last revision could be considered clear to the reader who would not necessarily be familiar with the manner in which GlaxoSmithKline Consumer Healthcare coded its promotional items. Furthermore, the prescribing information was marked as being last revised in January 2004. This would mean that the prescribing information was apparently revised after the Clinical Guide was last printed.

The clinical guide did not carry a clear date of last revision and furthermore the date contained within the unique code could not relate to the date the material was last revised due to the dates cited on the prescribing information. Pfizer Consumer Healthcare therefore alleged a breach of Clause 4.9.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated that promotional material must include the date on which the material was drawn up or last revised. The NiQuitin CQ Clinical Guide contained both. The date the material was drawn up was integral to the unique code NCQ/PW/0903/005; 0903 referred to the date drawn up. The prescribing information stated a revision date of January 04. GlaxoSmithKline Consumer Healthcare had never seen the year abbreviated to three digits (as in 005) so found this complaint disingenuous.

GlaxoSmithKline Consumer Healthcare did not consider this breached Clause 4.9.

PANEL RULING

The Panel noted that the Clinical Guide did not include a clear date of preparation. A date of last revision was given in the prescribing information as January 2004.

The Panel did not consider that use of the promotional code NCQ/PW/0903/005 was sufficient to satisfy the requirement of Clause 4.9 to include the date the promotional material was drawn up or last revised.

A further difficulty was that the promotional code indicated the material was drawn up in September 2003 which was not the date of preparation given that the prescribing information was last revised in January 2004.

Taking all the circumstances into account the Panel considered that GlaxoSmithKline Consumer Healthcare had not met the requirements of Clause 4.9 and thus a breach of that clause was ruled.

Complaint received **27 October 2004**

Case completed **7 January 2005**

CASES AUTH/1646/10/04, AUTH/1647/10/04 and AUTH/1663/12/04

HOSPITAL DOCTOR, PHARMACIST and ANONYMOUS v GLAXOSMITHKLINE

Sunday Times Asthma Supplement

A hospital doctor, a primary care trust (PCT) pharmacist and an anonymous complainant complained about a supplement on asthma which appeared in The Sunday Times. The front cover stated 'New approaches for the chance of a life without symptoms'; 'In association with GlaxoSmithKline' and the GlaxoSmithKline logo appeared in the bottom right-hand corner.

The supplement was a mixture of articles about asthma, advice on what to ask health professionals and case studies from patients/carers. The supplement focussed on combination therapy including details of the recently published GOAL (Gaining Optimal Asthma controL) study.

The only asthma medicine named in the supplement was GlaxoSmithKline's fixed combination product for asthma Seretide (salmeterol/fluticasone). The GOAL study compared Seretide with an inhaled corticosteroid. The supplement included a photograph of a patient holding a Seretide inhaler. The four case studies all featured patients taking Seretide.

All of the complainants alleged that the supplement advertised Seretide to the public. The hospital doctor additionally alleged that the supplement was covert advertising. The anonymous complainant was concerned that the supplement would create unachievable expectations for sufferers leading to disappointment and frustration with their current regimen which might lead them to reduce or discontinue treatment.

The Panel noted that the supplement had been sponsored by GlaxoSmithKline; it had been initiated by the company which had provided detailed direction as to the subject area to be covered as well as what was not to be covered. A copy of GlaxoSmithKline's overview and objectives document was given to all writers and sub-editors. GlaxoSmithKline had planned to distribute further copies of the supplement but on seeing the final item had decided not to proceed.

The Panel considered that GlaxoSmithKline was inextricably linked to the content of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation and content of the supplement. The Panel considered that GlaxoSmithKline was responsible for the content of the supplement in relation to compliance with the Code.

The Panel noted the summaries of discussions between GlaxoSmithKline's agency and The Sunday Times and considered that the discussions and approach were not consistent with the requirements of the Code that material for the general public must not promote a specific medicine and must be balanced. Notes from one meeting between the agency and The Sunday Times stated that the objective of the supplement was to provide a guaranteed communications platform from which to disseminate key Seretide/GOAL messages following publication of the [GOAL] data to consumers and health professionals. The supplement focussed on combination therapy but mention of competitor products was by generic name and there had to be no mention of flexible dosing, which was a feature of AstraZeneca's combination product Symbicort (formeterol/budesonide), or of Symbicort trial data.

The supplement discussed the GOAL study; Seretide was mentioned. One case study headed 'Free to play netball' highlighted the effect of Seretide on a young patient's life and included a photograph of her holding a Seretide inhaler. The Panel considered that the photograph of the patient with the Seretide inhaler together with the content of the supplement meant that it was an advertisement for a prescription only medicine to the public. The Panel ruled a breach of the Code as acknowledged by GlaxoSmithKline.

The Panel did not consider that the supplement presented the information in a balanced way and it would encourage members of the public to ask their doctor to prescribe a specific medicine. Thus the Panel ruled a breach of the Code as acknowledged by GlaxoSmithKline.

The Panel further considered that the supplement was disguised promotion and ruled a breach of the Code in that regard.

With regard to the allegation that the supplement created unachievable expectations for sufferers that would not be met for all, the Panel considered that its previous rulings covered this point and no further ruling was made.

A hospital doctor, primary care trust (PCT) pharmacist and an anonymous complainant all complained about a supplement on asthma which formed part of The Sunday Times of 24 October. The cover of the 12 page supplement stated 'New approaches for the chance of a life without symptoms'; 'In association with GlaxoSmithKline' and the GlaxoSmithKline logo appeared in the bottom right-hand corner.

The supplement was a mixture of articles about the disease, advice on what to ask health professionals and case studies from patients/carers. The supplement focussed on combination therapy including details of the recently published GOAL (The Gaining Optimal Asthma controL) study.

The supplement did not mention medicines by name apart from Seretide (salmeterol/fluticasone) which was GlaxoSmithKline's fixed combination product for asthma. The GOAL study compared Seretide with an inhaled corticosteroid.

The supplement included a photograph of a patient holding a Seretide inhaler. The four case studies all featured patients taking Seretide.

Case AUTH/1646/10/04

COMPLAINT

The hospital doctor alleged that the supplement contravened Clause 20 of the Code as it advertised a prescription only medicine, Seretide, to the public.

The complainant noted that the supplement contained approximately 19 individual items some of which solely provided accurate information about asthma, its symptoms, treatment etc.

At least five of the articles and a prominent photograph were devoted to the value of combination therapy. Two of the articles specifically referred to Seretide and the photograph showed a young patient happily displaying her Seretide inhaler. The other combination product available in the UK was not named and there was no picture of it. One article referred to the GOAL study but did not mention that this study was sponsored by GlaxoSmithKline. Combination therapy in the form of Seretide was promoted as the ideal therapy, despite the fact that the British Thoracic Society (BTS) and Scottish Intercollegiate Guideline Network (SIGN) Guideline on the Management of Asthma stated 'There is no difference in efficacy in giving inhaled steroid and long-acting ß2 agonist in combination or in separate inhalers'.

An article, illustrated by a man on a bicycle, provided patients with confused information and mixed messages. The headline stated that 'Combination therapy has replaced the inhaler'. The article itself, however, implied that by using 'combination therapy' it was possible to stop using inhalers. The patient was quoted as stating 'My inhaler has become almost redundant'. But it was not clear if he was referring to his combination inhaler or his reliever inhaler. The article also stated 'The latest combination therapies, where two different types of drugs are combined in one inhaler, are easier to use and increase the patient's chances of taking drugs regularly, thereby improving control of their asthma'. The article entitled 'Best in low doses' stated: '… combination therapy … make it a lot easier for the patient to use'. The BTS/SIGN Guideline however stated: 'Combination inhalers have not been shown to improve compliance in the medium to long term' which contradicted the article.

The complainant alleged that the supplement was covert advertising designed to encourage members of the public to ask their doctors to prescribe Seretide. This was in direct contravention of Clause 20.2 of the Code. The phrase 'In association with GlaxoSmithKline' was not clearly defined. The complainant queried how much of the cost of the supplement had been paid for by GlaxoSmithKline, and considered that the clear conflict of interest created by the fact that GlaxoSmithKline manufactured Seretide should have been prominently stated.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to the requirements of Clauses 10.1 and 20.1 as well as Clause 20.2 cited by the complainant.

Case AUTH/1647/10/04

COMPLAINT

The PCT pharmacist stated that he was shocked to be confronted with the supplement which in his opinion, was nothing short of direct advertising to patients. The complainant questioned whether this was in breach of the Code. The complainant noted that the supplement carried regular references to 'combination therapy' and one direct reference to Seretide with a picture of the patient holding up the product. The overall tone suggested that it was neither independent or balanced, suggesting at every opportunity that the combination product had advantages over others.

The complainant considered that this was a worrying development in the pharmaceutical industry's strategy to influence prescribing.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to the requirements of Clauses 20.1 and 20.2 of the Code.

Case AUTH/1663/12/04

COMPLAINT

The anonymous complainant stated that whilst some of it was helpful (albeit a re-hash of what was available through other easily accessible sources) the article about a young patient was nothing more than an advertisement for GlaxoSmithKline's product Seretide. It referred to dual therapy, it used the brand name twice in the text, it had a photograph of Seretide with the brand name clearly legible and it included the subjective patient comment 'Now it doesn't feel like I've got asthma'. This distorted use of patient case studies to sell the benefits of GlaxoSmithKline's combination product continued with two other such articles on the supplement.

The complainant did not know the detailed provisions of the Code but knew that companies were not allowed to advertise their products directly to the public.

The complainant stated that this was a cynical and blatant attempt to wrap up an advertisement as patient information, and was concerned that it would create unachievable expectations for sufferers leading to disappointment and frustration with their current regimen which might lead them to reduce or discontinue treatment.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to the requirements of Clauses 20.1 and 20.2 of the Code.

RESPONSE

Cases AUTH/1646/10/04, AUTH/1647/10/04 and AUTH/1663/12/04

GlaxoSmithKline stated that after seeing a previous industry sponsored supplement, it approached The Sunday Times, via a public relations (PR) agency at the beginning of 2004 to propose that a similar asthma supplement be produced later in the year. The

objectives were to provide a media platform from which to highlight suboptimal asthma management in the UK and communicate to patients and health professionals that more could and should now be achieved. In addition, GlaxoSmithKline wished to refer to the findings of a landmark trial in asthma. This trial demonstrated that a greater level of asthma symptom control than previously seen with any clinical study could be achieved, and would, therefore, provide context for an improved standard of asthma management to both patients and health professionals by demonstrating what might be possible in asthma management in the future. The PR agency was to provide The Sunday Times with information on GlaxoSmithKline (in terms of what the company did and what it wanted to achieve with the asthma supplement), why it had chosen The Sunday Times and why the article might interest its readership. Throughout the process, the PR agency liaised between GlaxoSmithKline and The Sunday Times. GlaxoSmithKline recognised that it was responsible under the Code for the conduct of agencies acting on its behalf.

Code considerations and copy approval

From the outset, it was made clear to the PR agency that GlaxoSmithKline was fully committed to the Code. This was to be an overriding consideration throughout all activities, and that this requirement should be clearly communicated to The Sunday Times.

Notes from an initial meeting between the PR agency and The Sunday Times clearly confirmed the above. The sections describing 'Key points' and 'Copy approval', specifically noted that the final copy of the asthma supplement was to be reviewed for ABPI approval by an independent, Times-appointed, panel.

'Key points

1 All editorial content is at the discretion of the Supplement Editor

2 The briefing stage is critical – once the brief has been signed off, GSK/[the PR agency] will have no influence over content

3 The copy will receive final ABPI approval from an independent review panel appointed by The Times

4 Need to decide whether to discuss treatments in terms of class or product (must mention all brands)

Copy approval

- Copy can not leave The Times building until publication
- Representatives from GSK/[the PR agency] [an asthma charity] can preview copy on-site
  - Overall content cannot be changed
- Final copy will be reviewed by independent Times appointed panel
  - Professor
  - Representative from ABPI'

This intent was echoed in notes from a second meeting between the PR agency and The Sunday Times, outlining the process and content, which stated the following:

'Implementation

- If Seretide is mentioned within the supplement, details of all competitor brands will also be mentioned. GSK/[the PR agency] must therefore establish if the supplement should discuss treatment in terms of class or product. If possible, mentioning of combination therapies would be the ideal route for the copy.
- The final supplement will receive ABPI approval by an independent review panel, appointed by the title. The appointed panel will include a Professor and a representative from the ABPI.
- Upon completion of the final copy GSK/[the PR agency]/third party group can preview the copy on-site at the titles offices, however, the copy can not leave the building until publication. NB. *At this stage of the process the overall content/angle of the supplement can not be amended but any inaccuracies or possible medicolegal problems can be amended.*

Supplement content

The title will want to ensure that the supplement is well-balanced and not overtly promotional towards Seretide. As such, clearly defined expectations should be set regarding what 'must' be included in the supplement in order to fulfil our objectives and what would be 'nice to have'.'

An Overview and Objectives document, dated 18 August, which summarised the discussions, stated:

'Product positioning

In line with the ABPI, Seretide and competitor products should be mentioned in a balanced way in appropriate sections. Any competitor products mentioned in the supplement should be mentioned by generic name only. Seretide should be mentioned in association with the new landmark clinical trial data.

Within the supplement there should be **no** mention of the following:

- GOAL without a reference to Seretide (as this is required by ABPI guidance).
- Mention of other combination treatments in relation to GOAL.
- Concept of flexible dosing.
- Any Symbicort trial data.
- Any other trial data that is not strongly relevant to the story.

Considerations

- In order to proceed with the development of the supplement GSK/[the PR agency] would like to be notified of the individuals who will form the independent ABPI approval panel.
- Once the objectives and content of the supplement are agreed and put into writing, they should be

adhered to by both GSK/[the PR agency] and The Sunday Times.

- As previously discussed we understand that GSK/[the PR agency] will have full control over the design and layout of the front cover.
- We would like to discuss the choice of author for the supplement.

GSK strictly adhere to the ABPI code of practice. The contents of this brief have been reviewed and approved by GSK medical therefore we do not anticipate that the independent review panel should highlight any ABPI issues.'

GlaxoSmithKline noted that an email sent by The Sunday Times demonstrated that The Sunday Times understood that the primary intent of the asthma supplement was to inform readers about the condition, to raise awareness regarding treatment aims and to do so within the Code:

'The focus of the supplement is to educate and inform readers (patients and medical professionals) about what asthma is, how badly it affects lives in the UK, how asthma how treatment can be improved to a level where sufferers can live symptom-free. This is due to a medical regime using Seretide, but, in accordance with the guidelines, we will not use the brand-name Seretide unless we are writing about what GOAL says about it, the rest of the time we will use generic names. I have a copy of your 'overview and objectives' document, which will be given to all writers and sub-editors, and the Glaxo team will provide the final checks, so I am confident we will meet all your objectives safely within the ABPI guidelines.'

GlaxoSmithKline submitted that this was re-iterated in the Final Brief document dated 1 September 2004. From the above it could be seen that the intent of the piece was to provide balanced information as well as setting expectations regarding improvements in asthma management. This correspondence was conducted in the context of internal GlaxoSmithKline guidance on preparation and approval of PR materials.

As agreed, GlaxoSmithKline was permitted to review the written copy at The Sunday Times offices on 7 October to check for factual inaccuracies, bearing in mind that editorial content was at the discretion of the supplement editor, and that there would be a further check for compliance with the Code by an independent ABPI review panel prior to the anticipated print date of 17 October.

GlaxoSmithKline submitted that reasonable steps were taken to ensure that all parties involved in the production of the supplement understood the importance of adherence to the Code. In retrospect, however, GlaxoSmithKline acknowledged that there were several areas where it could have been more robust in its adherence to the Code and its internal guidance. Specifically [ABPI] approval should not have been delegated to The Sunday Times, and although the intent was to achieve a balanced picture of asthma and possibilities for new treatments whilst setting the new data from the GOAL study in context, the delegation of final responsibility did not allow GlaxoSmithKline sufficient control to be able to ensure this.

GlaxoSmithKline noted that there was an error in the briefing document where it stated that there should be no reference to GOAL without reference to Seretide. This should have read, 'no reference to Seretide without reference to GOAL.' GlaxoSmithKline acknowledged that this might have contributed to the confusion in the minds of the journalists.

Authorship of asthma supplement

All articles in the supplement were written by the authors themselves. None were ghost written by either GlaxoSmithKline or a third party, and there was no known relationship between the authors and either GlaxoSmithKline or the PR agency. The Sunday Times commissioned the authors; notes from a meeting on the 21 July stated 'The title will commission an author to develop the supplement.' In these notes, the PR agency suggested an author known to GlaxoSmithKline however The Sunday Times was not obliged to engage this author. In fact, this author wrote two articles for the supplement neither of which mentioned Seretide, the GOAL study or any other GlaxoSmithKline medicine. The Overview of Objectives document noted that the PR agency wished to discuss the choice of author for the supplement with The Sunday Times, however the email sent by The Sunday Times confirmed that The Sunday Times made the choice of authors:

'The supplement will be written mainly by [a named author], he and I will choose suitably qualified journalists for the bits he can't do. They will talk to experts in medicine, asthma charities, etc, for our information. Anyone you can suggest/provide will be helpful, though I am sure [the author] has an excellent contacts book already. Though we will need your help with case studies'

Four case studies were used. The PR agency approached the individuals to ask if they would be prepared to be interviewed by The Sunday Times for an asthma supplement. If they were, then the PR agency forwarded their contact details to The Sunday Times and took no further part in the proceedings. No copy or pictures relating to the case studies, or any other article included in the asthma supplement, were provided by either the PR agency or GlaxoSmithKline.

Pictures in asthma supplement

The image, title and subtitle for the front cover only were chosen in consultation with the PR agency, acting on behalf of GlaxoSmithKline. The front cover was reviewed by GlaxoSmithKline at The Sunday Times offices on 7 October, and considered to comply with the Code. The written copy was reviewed for factual accuracy at that time, and only factual inaccuracies were permitted to be changed by the editorial team at The Sunday Times. No images other than those on the front cover were available for review by GlaxoSmithKline at that time, and therefore, it was a matter of grave concern and disappointment to GlaxoSmithKline to discover a photograph of a Seretide Accuhaler in the supplement, that was so clearly outwith the Code.

This was an unwitting error for which GlaxoSmithKline recognised its accountability.

Financing of asthma supplement

The asthma supplement was commissioned by GlaxoSmithKline, via its PR agency. Details of the costs were provided. Once GlaxoSmithKline saw the published asthma supplement, it did not proceed with the online version, or any further distribution.

Explanation of the meaning 'In association with GlaxoSmithKline'

This was considered the most appropriate term since GlaxoSmithKline had commissioned the supplement, but did not have editorial control. This term had been used for the previously referred to industry sponsored supplement, and was therefore considered acceptable.

Conclusions

GlaxoSmithKline remained fully committed to the Code and this was its overriding consideration throughout all activities associated with the production of the asthma supplement. GlaxoSmithKline submitted that reasonable steps were taken to ensure that the supplement would comply with the Code, however in retrospect it recognised that in trying to remain distant from final editorial control, and allowing third parties to undertake these activities that this was not achieved. Additionally it recognised that an error within the briefing document might have resulted in a different objective in the minds of the journalists. As such it recognised that Seretide might have been given greater prominence than intended by the journalists who authored articles according to GlaxoSmithKline's brief. GlaxoSmithKline however re-emphasised that at the point of final review it was only permitted to correct factual inaccuracies, and that no images other than the cover image were seen by GlaxoSmithKline in advance of publication.

GlaxoSmithKline recognised that the article did not achieve the desired level of balance and as such it admitted a breach of Clause 20.2 of the Code. In breaching Clause 20.2 it recognised that there was greater prominence of Seretide than intended and regretfully also admitted a breach of Clause 20.1.

Key learnings and remedial actions

GlaxoSmithKline decided to remain as 'hands off' as possible once the article had been briefed to journalists and it was anticipating that the content would, after review by GlaxoSmithKline, be checked once more for Code compliance prior to print. In reality, the error in the briefing material and the inability to finally approve the written copy left GlaxoSmithKline exposed as liable for breaches of the Code, because it did not have access to the final version of the asthma supplement. It acknowledged its responsibilities and duties in connection with this issue and had therefore investigated in detail all steps of the process and its relationship with the agency and the Sunday Times.

Summary

GlaxoSmithKline intended to commission an ethical, balanced, educational supplement. It played no part in the writing of the supplement, nor did it provide any photographs or visual materials. Editorial control was completely in the hands of The Sunday Times. GlaxoSmithKline attempted to ensure that appropriate control and sign off would occur at each stage of development. The initial expectation of an independent approval panel (provided by The Sunday Times) did not materialise. By respecting journalistic independence (insisted upon by The Sunday Times) GlaxoSmithKline ultimately had limited power to amend copy apart from factual inaccuracy, and was not given the opportunity to approve the full and complete final version. GlaxoSmithKline saw the final supplement when it was too late to stop distribution. Unintentionally the item had a promotional appearance. GlaxoSmithKline accepted that the final version was in breach of Clauses 20.1 and 20.2. This was not the intention. GlaxoSmithKline accepted its responsibility in commissioning this supplement and had undertaken an appropriate internal investigation and review

Case AUTH/1646/10/04

With regard to the allegation that 'the supplement was covert advertising', GlaxoSmithKline denied that this was so on two counts. Notwithstanding the non-promotional intent of the supplement, in addition, the declaration that the supplement was produced in association with GlaxoSmithKline was clearly evident on the front cover of the supplement, and the reader would be aware of this from the outset.

Case AUTH/1663/12/04

With regard to the complainant's statement that 'this was a cynical and blatant attempt to wrap up an advertisement as patient information …', GlaxoSmithKline's stated that its intent was to achieve a balanced picture of asthma and possibilities for treatment. Unfortunately the company's lack of editorial control, inability to approve the full and complete final version of the supplement and the obvious absence of the Times-appointed independent review panel checks for ABPI compliance, resulted in combination therapy and Seretide being given greater prominence than intended. GlaxoSmithKline repeated that editorial control was solely within the remit of The Sunday Times, and that it had no control over images other than those on the front cover. GlaxoSmithKline recognised that it was responsible for the conduct of its agencies acting on its behalf, nevertheless, it was disappointed to discover a Seretide brand image that was so at variance with its intent for the supplement.

With regard to the complainant's concern that the supplement would 'create unachievable expectations for sufferers… leading to disappointment and frustration with their current regimen which might lead them to reduce or discontinue treatment', GlaxoSmithKline stated that large, multi-national, community based surveys had confirmed that current levels of asthma control were poor when assessed against the recommendations of national and

international guidelines. The AIRE Survey (Asthma Insights and Reality in Europe) had demonstrated that only 5.3% of patients were currently well controlled when assessed against the GINA (Global Initiative for Asthma) guidelines, and a UK based study (King *et al* 2000) had shown that 70-80% of patients were not well controlled when assessed against the British Guideline on Asthma Management. In consequence, it had been suggested that guideline-defined asthma control was unrealistic for the majority of patients. GlaxoSmithKline's objectives for the supplement were to provide a media platform from which to highlight suboptimal asthma management in the UK, and to tell patients and health professionals that more could and should now be achieved.

GlaxoSmithKline stated that if the supplement had raised awareness of the condition among patients diagnosed with asthma, or had served to prompt patients whose asthma was not adequately controlled to seek advice, then it would have achieved its objectives. GlaxoSmithKline refuted the complainant's supposition that the overall tone and content of the supplement was such as to create unachievable expectations that might lead to treatment discontinuation; rather, that patients were more likely to seek appropriate advice and treatment from their healthcare team. In this regard GlaxoSmithKline noted several educational pieces within the supplement.

PANEL RULING

The Panel considered that in all three cases, its ruling in a similar case, Case AUTH/1644/10/04, was relevant.

Panel ruling in Case AUTH/1644/10/04

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. In the case of sponsored material aimed at the general public consideration would also have to be given to the requirements of Clause 20.

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The supplement in question had been sponsored by GlaxoSmithKline. The supplement had been initiated by the company which had provided detailed direction as to the subject area to be covered as well as what was not to be covered. A copy of GlaxoSmithKline's overview and objectives document was given to all writers and sub-editors. GlaxoSmithKline had planned to distribute further copies of the supplement but once seeing the final item had decided not to proceed.

The Panel considered that GlaxoSmithKline was inextricably linked to the content of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation and content of the supplement. The Panel considered that GlaxoSmithKline was responsible for the content of the supplement in relation to compliance with the Code.

The Panel noted the summaries of discussions between GlaxoSmithKline's agency and The Sunday Times and considered that the discussions and approach were not consistent with the requirements of either Clause 20.1 or Clause 20.2 that material for the general public must not promote a specific medicine and must be balanced. The Panel noted that the outline of process and content document dated 21 July stated that the objective of the supplement was to provide a guaranteed communications platform from which to disseminate key Seretide/GOAL messages following publication of the [GOAL] data to consumers and health professionals. The supplement focussed on combination therapy but mention of competitor products was by generic name and there had to be no mention of flexible dosing which was a feature of AstraZeneca's combination product Symbicort (formeterol/budesonide) or Symbicort trial data.

The supplement discussed the GOAL study; Seretide was mentioned. One case study headed 'Free to play netball' highlighted the effect of Seretide on a young patient's life and included a photograph of her holding a Seretide inhaler.

The Panel considered that the photograph of the patient with the Seretide inhaler in the supplement together with the content of the supplement meant that it was an advertisement for a prescription only medicine to the public. The Panel ruled a breach of Clause 20.1 of the Code as acknowledged by GlaxoSmithKline.

The Panel did not consider that the supplement presented the information in a balanced way and it would encourage members of the public to ask their doctor to prescribe a specific medicine. Thus the Panel ruled a breach of Clause 20.2 of the Code as acknowledged by GlaxoSmithKline.

Case AUTH/1646/10/04

The Panel considered that its rulings of a breach of Clauses 20.1 and 20.2 of the Code applied here.

With regard to the alleged breach of Clause 10.1, the Panel considered that the supplement was disguised

promotional material and thus a breach of that clause was ruled.

Case AUTH/1647/10/04

The Panel considered that its rulings of a breach of Clauses 20.1 and 20.2 of the Code applied here.

Case AUTH/1663/10/04

The Panel considered that the present case was similar to Case AUTH/1644/10/04. In addition the complainant had alleged that the supplement created unachievable expectations for sufferers that would not be met for all. The Panel noted GlaxoSmithKline's response on this point. The Panel considered that this allegation was covered by its ruling in Case AUTH/1644/10/04 and thus considered that its rulings of breaches of Clauses 20.1 and 20.2 of the Code applied here.

Case AUTH/1646/10/04

Complaint received **28 October 2004**

Case completed **21 January 2005**

Case AUTH/1647/10/04

Complaint received **29 October 2004**

Case completed **21 January 2005**

Case AUTH/1663/10/04

Complaint received **6 December 2004**

Case completed **9 February 2005**

CASE AUTH/1649/10/04 *NO BREACH OF THE CODE*

PRIMARY CARE TRUST PRESCRIBING ADVISER v WYETH

Promotion of Prostap SR

The lead prescribing adviser to a primary care trust (PCT) alleged that Wyeth had promoted Prostap as an alternative to AstraZeneca's Zoladex without making it clear that the two were not always interchangeable. Although both were licensed for use in patients with prostate cancer, only Zoladex could additionally be used in breast cancer. The complainant noted that a general practice within the PCT had agreed to blanket switch all patients on Zoladex to Prostap SR. One of the patients changed to Prostap was a woman receiving Zoladex for breast cancer. The complainant considered that since Wyeth promoted change, it had a moral duty to help ensure that only appropriate changes occurred and that it highlighted those indications for which Zoladex was licensed but Prostap was not.

The Panel noted that the Code required pharmaceutical companies to promote their own medicines in a responsible, ethical and professional manner. The Code did not necessarily require a company to highlight every difference between its medicine and a competitor.

Wyeth provided copies of the promotional material for Prostap 3 and Prostap SR. The Prostap 3 material was headed 'In advanced prostate cancer'. An objection handler 'A simple switch to Prostap' featured five bullet points of equal prominence. The Panel was concerned that because the indication, advanced prostate cancer, in the first bullet point did not stand out from the rest of the text there was a possibility that the subsequent bullet points which did not restate the indication but which referred to switching patients from Zoladex, might be assumed to apply to all patients which was not so. Similarly in a second objection handler, 'Patients prefer Prostap', the indication was again clearly stated in the first sentence but it did not stand out from the rest of the text which referred to switching patients from Zoladex to Prostap. The Panel considered that it would have been helpful for the indication to have been more prominently stated and asked that Wyeth be advised of its concerns in this regard. However both objection handlers were 'watermarked' with photographs of men, neither mentioned or alluded to breast cancer and so the Panel considered that overall there was no implication that patients other than those with advanced prostatic cancer could be switched from Zoladex to Prostap 3. A detail aid 'Give the comfort of Prostap' dealt with the management of endometriosis. Page 4 compared the needle sizes of Prostap SR and Zoladex and there was an implication that patients could be switched to Prostap SR because the injection might be less uncomfortable. Again there was nothing to suggest that breast cancer patients should be switched. The representatives' briefing material similarly did not suggest that Prostap could be used in breast cancer as an alternative to Zoladex.

The Panel acknowledged that it had no details of the discussion between the representative and the practice that had switched patients in error. If a representative had said or implied that all Zoladex patients could be switched to Prostap then this would be in breach of the Code. In the Panel's view the statements and inferences made about switching patients from Zoladex to Prostap in the materials were within the therapeutic areas of advanced prostatic cancer or endometriosis. There was no

mention or inference that breast cancer patients could be so switched. The Panel ruled no breach of the Code.

The lead prescribing adviser to a primary care trust (PCT) complained about the promotion of Prostap SR (leuprorelin acetate, one month depot injection) by Wyeth Pharmaceuticals. Prostap SR was indicated for, *inter alia*, treatment of advanced prostatic cancer and the management of endometriosis. Wyeth also marketed Prostap 3 which was a three month depot injection indicated for the management of advanced prostatic cancer only.

COMPLAINT

The complainant stated that Prostap SR was aggressively marketed as an alternative to AstraZeneca's product Zoladex with the advantages of being an easier injection and less expensive (discounted price). What was lost in the marketing were the different indications for the two products.

Zoladex and Prostap were both most commonly used in prostate cancer and many professionals were unaware of other indications for its (sic) use. It had recently been noted that a general practice within the PCT had agreed to blanket switch all patients on Zoladex to Prostap SR. The switch was in response to marketing around its benefits largely influencing nursing staff who then conveyed the benefits to the GPs. The practice switched all patients as the two products were thought to be interchangeable. One of the patients changed to Prostap was a woman who was receiving Zoladex for breast cancer. Prostap was not licensed for breast cancer but the practice was unaware of this difference in product licences.

The complainant wrote to raise attention to the potential for patients' lives being put at risk if Prostap SR was not marketed responsibly with due attention to its licensed indications.

When writing to Wyeth, the Authority asked it to respond in relation to Clauses 2, 7.2, 9.1, 15.2 and 18.1 of the Code and to give details of the switch programme for Prostap SR.

RESPONSE

Wyeth disagreed with the complainant's statement that Prostap SR was 'aggressively marketed as an alternative to Zoladex'. All Prostap promotional materials approved for use by Wyeth were accurate, balanced, fair, objective and unambiguous as required by Clause 7.2 of the Code. Part of the promotional platform for Prostap included displacement points against Zoladex which was currently the luteinizing hormone-releasing hormone (LHRH) analogue market leader in the UK for prostate cancer and endometriosis. This promotional activity was normal business practice and, as stated above, was carried out in compliance with Clause 7.2. The Wyeth representative who covered the GP practices within the complainant's PCT promoted Prostap 3 for advanced prostatic cancer and did not promote Prostap SR as alleged. Prostap SR materials promoted the product for endometriosis.

Wyeth noted that the complainant had stated that Prostap SR was being marketed as 'an easier injection' than Zoladex. The needles used to administer Prostap and Zoladex were compared (eg ZPR0910) but this was done in compliance with Clauses 7.2, 7.3 and 7.4.

Wyeth noted that the complainant had further alleged that Prostap was being promoted as 'less expensive (discounted price)' than Zoladex. Wyeth did discount Prostap. However, Prostap might be less expensive than Zoladex in a given locality depending on the discount offered by AstraZeneca.

Wyeth stated that Prostap SR and Prostap 3 were promoted within their licensed indications only. It was clearly stated on the front cover of the Prostap 3 materials 'In advanced prostate cancer' which reflected the product's only licensed indication. The Prostap 3 detail aid (ref ZPRO910) promoted switching to Prostap 3 and stated 'Switching patients *with advanced prostate cancer* to Prostap 3 is straightforward, and can be carried out with no delay in therapy' (emphasis added). It was therefore clear which patients were appropriate to switch to Prostap 3. The Prostap SR materials clearly promoted the product for endometriosis due to the 'endometriosis' statement on the front cover and the content of the detail aid and leavepiece (refs ZPRO805 and ZPRO825). Wyeth therefore rejected the complainant's statement that the different indications for the two products were lost in its marketing.

Wyeth noted that the complainant had further alleged that 'many professionals were unaware of other indications for its use'. As described above, Wyeth representatives promoted Prostap 3 and Prostap SR using the approved promotional materials only. These materials were very clear as to the indications for which the products were promoted and full details of both were also set out in their respective summaries of product characteristics (SPCs), which were available to health professionals.

Wyeth did not know of a GP practice which had agreed to blanket switch all patients on Zoladex to Prostap SR as described by the complainant. Wyeth noted that it had not been provided with any evidence to substantiate the allegations made in this respect. If there had been such a blanket switch, this took place without the knowledge or involvement of the Wyeth representative, and consequently Wyeth had no case to answer in this respect. Moreover, the prescribing decision to switch patients to a given medicine clearly lay with the GP(s) involved, as did any resultant liability. Only GPs could decide the best treatment for their patients, taking into account their patient's medical condition, medical history and the relevant product details (in the respective SPC). Wyeth considered it was both unreasonable and unfair to health professionals in this (or any other) area of medicine to suggest that they would prescribe either Zoladex or Prostap without knowing the relevant indications of those products. It was therefore deeply concerning to hear that a practice had blanket switched its patients without taking into account these highly relevant considerations.

Wyeth noted that although it produced a Nurse Patient Care Pack (refs ZPRO911 and ZPRO912),

which had been approved as Code compliant, for distribution to practice nurses and specialist nurses, the Wyeth representative referred to above did not use this pack in her territory.

Wyeth did not consider that there was any evidence to support the allegation that it was not marketing Prostap SR responsibly with due attention to its licensed indications. The prescribing information was included on all the promotional materials.

In conclusion Wyeth stated that the only promotional materials/activities employed by representatives comprised the prostate cancer and gynaecology detail aids and leavepieces. The detailing provided by the representative strictly adhered to the prostate cancer and gynaecology materials that, as outlined above, clearly stated the licensed indications.

FURTHER COMMENTS FROM THE COMPLAINANT

The response from Wyeth was sent to the complainant for comment. In response the complainant noted that Wyeth stated that it commented on the different needles sizes for Prostap and Zoladex. Anecdotally the complainant had heard professionals ask 'Which would you prefer?' The complainant also noted Wyeth's submission that its representatives only promoted Prostap SR and Prostap 3 within their licenced indications.

The complainant did not question the quality of the Wyeth representative or that the information used was directly in breach of regulations. However, the complainant considered that Wyeth had a moral duty to ensure that health professionals understood that Zoladex and Prostap were not always mutually interchangeable.

The complainant noted that Wyeth acknowledged that Zoladex was the market leader and that its promotional activity was in line with accepted regulations. However, since Wyeth promoted change, it had a moral duty to help ensure that only appropriate changes occurred and that it highlighted those indications for which Zoladex was licensed but its products were not.

The complainant stated that the PCT had had a large practice switch; all patients on Zoladex to Prostap SR, including a patient who was being treated for breast cancer. The patient received a supply of Prostap SR which was noted by the complainant when the practice contacted her to check whether Prostap 3 could be used for breast cancer as it was thought that it might be easier for the patient to have less frequent injections. The message about the different licensing indications was lost and this potentially put the patient at risk. This practice was committed to quality patient care and the complainant did not regard this error reflected poor clinical governance. The GP thought that the products were interchangeable and he and his partners had agreed to the blanket switch. The practice had handled this as a critical incident and the complainant had reported it through the PCT internal incident procedures as well as sending out prescribing alerts to raise awareness of the issue.

The complainant was concerned that this did not happen again.

It was important to realise that these products were usually started in secondary care and many GPs had only restricted knowledge of them though they were often prepared to prescribe them even without formalised shared care. Sometimes it was only when an incident happened that there was recognition of learning needs.

FURTHER COMMENTS FROM WYETH

In response to a request for further information Wyeth stated that due to the simplicity of the key selling messages for Prostap (ie comparative needle size/acceptability and price) formal written briefing documents had not been produced. However, representatives were provided with the key sales messages, on an ongoing basis with updates related to recent literature and guidance such as that produced by the National Institute for Clinical Excellence (NICE). Wyeth provided copies of documents in use at the time of the complaint; these included, 'Key sales messages', NICE guidance on cancer services 'Improving Outcomes in Urological Cancers', September 2002 and details of two studies on needle size and patient tolerability.

PANEL RULING

The Panel noted that the complainant considered that Wyeth's promotion of Prostap SR had not adequately drawn attention to the fact that its licensed indications were not the same as those for Zoladex. There would be some patients, notably women with breast cancer, who could not be switched from Zoladex to Prostap SR.

The Panel noted that the Code required pharmaceutical companies to promote their own medicines in a responsible, ethical and professional manner. Information, claims and comparisons must be accurate, balanced, fair, objective and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication. The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC. The Code did not necessarily require a company to highlight every difference between its medicine and a competitor.

Wyeth provided copies of the promotional material for Prostap 3 and Prostap SR. The Prostap 3 material was headed 'In advanced prostate cancer'. An objection handler 'A simple switch to Prostap' (ref ZPR0905) featured five bullet points of equal prominence. Although the first bullet point stated 'Switching patients with advanced prostate cancer to Prostap 3 is straightforward and can be carried out with no delay in therapy' the indication was not restated in any of the following bullet points. The Panel was concerned that because the indication in the first bullet point did not stand out from the rest of the text there was a possibility that the subsequent bullet points, which referred to switching patients from Zoladex, might be assumed to apply to all patients which was not so. Similarly a second objection handler 'Patients prefer Prostap' (ref

ZPR0907) began with 'A study in advanced prostate cancer compared the tolerability of Prostap SR and [Zoladex]' and although the indication was again clearly stated it did not stand out from the rest of the text which referred to switching patients from Zoladex to Prostap. The Panel considered that it would have been helpful for the indication to have been more prominently stated and asked that Wyeth be advised of its concerns in this regard. However both objection handlers were 'watermarked' with photographs of men, neither mentioned or alluded to breast cancer and so the Panel considered that overall there was no implication that patients other than those with advanced prostatic cancer could be switched from Zoladex to Prostap 3. A detail aid 'Give the comfort of Prostap' (ref ZPR0805) dealt with the management of endometriosis. Page 4 compared the needle sizes of Prostap SR and Zoladex and there was an implication that patients could be switched to Prostap SR because the injection might be less uncomfortable. Again there was nothing to suggest that breast cancer patients should be switched.

The representatives' briefing material similarly did not suggest that Prostap could be used in breast cancer as an alternative to Zoladex. The 'Key sales messages' document was clearly headed 'Prostap urology primary care'; the NICE guidance referred to outcomes in urological cancers and of the two studies on needle size and patient tolerability one had been published in the Journal of Prostatic Cancer and Prostatic Diseases and the other mentioned no clinical indication at all.

The Panel acknowledged that it had no details of the discussion between the representative and the practice that had switched patients in error. If a representative had said or implied that all Zoladex patients could be switched to Prostap then this would be in breach of the Code. In the Panel's view the statements and inferences made about switching patients from Zoladex to Prostap in the materials were within the therapeutic areas of advanced prostatic cancer or endometriosis. There was no mention or inference that breast cancer patients could be so switched. The Panel ruled no breach of Clauses 2, 7.2, 9.1 and 15.2.

Complaint received **1 November 2004**

Case completed **3 February 2005**

CASE AUTH/1650/11/04

HOSPITAL CONSULTANT v WYETH

Conduct of representatives

A hospital consultant complained about the activities of representatives from Wyeth, noting that the company held a local reputation for wining and dining NHS staff. The complaint referred to a meeting at a restaurant attended by hospital staff which had no scientific or educational content. The complainant alleged that such social events were used as inducements to gain access to junior medical staff.

The complainant provided a poster announcing the meeting which had been displayed in a public area of the hospital. The poster consisted of an advertisement for Zoton FasTab beneath which appeared the text 'are taking us to [a named] restaurant for dinner and drinks PRHO [pre-registration house officer] Payday Night Out!!' and 'It's brilliant …. Wyeth are paying for everything!!!'.

The Panel noted Wyeth's submission that the meeting featured on the poster had been organised by a representative acting outside of the company's standard operating procedure. The representative had taken health professionals to dinner in a public restaurant. The evening was a social event and advertised on this basis. There was no educational content. The Panel considered that the representative had failed to maintain a high standard of ethical conduct; she had not followed company policy nor had she complied with all relevant requirements of the Code. Although the representative had been trained the events were so clearly outwith the Code that the Panel considered that the company had not maintained a high standard. Breaches of the Code were ruled. The Panel considered that the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted that the representative had first learned about the existence of the poster at the dinner itself. The Panel noted that the dinner was informally organised by one of the junior house officers (JHO) at the representative's request. Although the representative had thus delegated responsibility for some of the organization of the meeting she nonetheless remained responsible for it. Companies could not delegate their responsibilities under the Code to third parties. The poster incorporated an advertisement for Zoton FasTab the display of which in the public area meant that a prescription only medicine had been promoted to the public. A breach of the Code was ruled.

The Panel considered that it was difficult to determine where the truth lay with regard to the alleged use of the social functions to gain interviews with the junior medical staff. The Panel noted that there was no evidence in this regard although the provision of the hospitality might make the junior medical staff more likely to see the Wyeth representative. The Panel had no option other than to rule no breach of the Code.

The complainant alleged that Wyeth representatives wandered around local hospitals, including clinical areas, in the expectation of meeting hospital staff without prior appointment which was in breach of local policy.

The Panel noted that no details had been provided. If such events occurred this would be outside hospital policy. The allegation was denied by Wyeth. The Panel had no option other than to rule no breach of the Code.

The complainant further noted that lansoprazole (Zoton) had been prescribed more often recently despite omeprazole being the local proton pump inhibitor of choice. A number of prescribers had reported that Wyeth representatives had indicated that lansoprazole was number one on the formulary, which was not so.

Wyeth had verbally informed representatives about the formulary choice in May/June 2004 and they were shown the open access hospital web pages from which they could download the formulary. The Panel queried, given the confusion, whether it was sufficient to verbally instruct representatives about the local formulary. It would have been helpful if the representatives had been given details of the formulary and clear written instruction as to what could be said about lansoprazole in relation to it. Although lansoprazole prescribing had increased despite the formulary, the Panel considered that it had no option other than to rule no breach of the Code.

A hospital consultant complained about the activities of representatives from Wyeth Pharmaceuticals.

COMPLAINT

The complainant stated that Wyeth's actions had raised concerns amongst several hospital, general practitioners and pharmacy colleagues.

Wyeth held a local reputation for wining and dining NHS staff. Representatives initiated bookings at a local restaurant and informally invited groups of staff (junior doctors, pharmacists, general practitioners, or primary care practice managers). Typically, the representative supplied unrestricted food and alcohol, with no attempt to incorporate any informative or educational component. These social events occurred frequently. The most recent noted by the complainant involved around thirteen pre-registration medical staff from a local hospital who were invited to a restaurant on 28 October. Wyeth's representative had approached some staff directly on hospital wards, and invited others by word-of-mouth. No scientific, promotional or educational component was included in the evening whatsoever, only gratuity by way of free dinner and copious amounts of alcohol. Many of the attendees indicated to the complainant that they had recently received similar gratuities from Wyeth.

The complainant stated that details of similar social events were not included as the event described above was representative.

The complainant alleged breaches of the Code in that the meeting on 28 October was a wholly social event, and that Wyeth had failed to maintain a high standard of conduct. The complainant further alleged

that the dinner and drinks parties hosted by Wyeth, as outlined above, had been used as inducements to gain access to junior medical staff in breach of the Code.

The complainant subsequently provided a copy of an advertisement which he stated had been attached to the wall outside the medical wards, on full display to hospital staff, patients and visitors or other members of public. The poster consisted of an advertisement for Zoton FasTab beneath which appeared the text 'are taking us to [a named] restaurant for dinner and drinks PRHO [pre-registration house officer] Payday Night Out!! It also stated 'Its brilliant…Wyeth are paying for everything!!! Put names on list in [ward] doctors room'. The complainant stated that the detail was self-explanatory, and emphasised the frivolous approach that had become so closely associated with the local Wyeth marketing machine.

Other problems had been raised by the complainant's colleagues two of which deserved mention. Admittedly, it was difficult to specify the exact times and individuals involved. However, the annoyance that the Wyeth representatives had caused over recent weeks and months had been such that a number of medical and hospital pharmacy staff were prospectively monitoring future occurrences, as follows:

Wyeth representatives had been noted on several occasions to wander around local hospitals, including clinical areas, in the expectation of meeting hospital staff without prior appointment. This was a particular problem at two local hospitals. This was in breach of trust policy, details of which had been supplied to Wyeth representatives (a copy was provided).

Increasing numbers of prescriptions for lansoprazole had been initiated over recent months in the local area, in spite of the local formulary stipulation that omeprazole was the proton pump inhibitor of choice. A number of primary and secondary care prescribers reported that Wyeth representatives had indicated 'lansoprazole was number one on the formulary', which was blatantly untrue. The complainant was unclear whether this reflected ignorance on the part of the sales team, or misrepresentation. In either case, Wyeth was working against the premise of formulary-based prescribing and had been undermining the efforts of the local pharmacy-based formulary implementation team.

The complainant sincerely hoped that Wyeth recognised the detrimental effect its actions had had on local NHS activity, and the potentially negative impact this could have on relationships between the NHS and the pharmaceutical industry. The complainant hoped that Wyeth would make some effort to put things right.

When writing to Wyeth, the Authority asked it to respond in relation to Clauses 2, 7.2, 9.1, 15.2, 15.3, 15.4 and 19.1 and 20.1 of the Code.

RESPONSE

Wyeth noted that the complaint related to a meeting held on 28 October. Wyeth took its meetings and hospitality procedure extremely seriously, as could be seen in its standard operating procedure (SOP) 1.13.

This SOP clearly stated the requirements for meetings held in restaurants, including:

1 For all meetings initiated by the company, formal invitations and agendas must be issued prior to the meeting by the sales representative.

2 All arrangements for meetings and materials relating to meetings would be reviewed by the RBM [regional business manager; representative's manager].

3 The educational content must be the main purpose of the meeting and the hospitality must be secondary to the purpose of the meeting.

4 A private room should be used.

5 The level of hospitality must be appropriate and not out of proportion to the occasion, and costs could not exceed the level which recipients would normally adopt when paying for themselves. A general guideline was that up to £10 a head would be acceptable for lunchtime, and up to £40 (including drinks) per head for the evening.

Wyeth stated that company procedure was not followed with respect to the first four points above. Regarding the fifth point, the cost per head was £32.84 (total £459.69) which was below the £40 limit specified in SOP 1.13. The key facts were:

1 The evening meeting was informally organised by a junior house officer (JHO), following a series of postgraduate lunchtime educational meetings that took place on 2 August, 25 August and 20 October.

2 The JHO gathered a list of attendees of these lunchtime meetings, and arranged a date for the evening meeting.

3 There was no substantive educational content at the evening meeting.

4 No RBM approval was sought by the representative for this meeting.

Clearly, and regrettably, the representative's actions contravened Wyeth's meetings and hospitality procedure, and it therefore accepted breaches of Clauses 15.2 and 19.1. Wyeth did not, however, accept breaches of Clauses 2 and 9.1, because:

1 The representative was trained regarding Wyeth's SOPs including SOP 1.13, and was sent a copy of this SOP (signed receipts provided).

2 Wyeth provided extensive training to all of its representatives, and signed training logs were enclosed, together with relevant training materials.

3 The representative did not seek approval from their RBM for the meeting, so the RBM was unable to take corrective action.

4 Following this complaint, Wyeth promptly instigated appropriate SOP refresher training for the entire UK sales force (this was currently in process).

Wyeth made every effort to ensure that its sales force behaved in a highly professional manner and in compliance with the Code. Wyeth took any complaint extremely seriously, and would respond accordingly. However, it did not consider that the company had

breached Clauses 2 or 9.1, as all reasonable steps were taken to ensure Code compliance, and robust and verifiable procedures were in place. In this context, Wyeth did not accept that the failings of a single representative who had been thoroughly and verifiably trained in accordance with robust SOPs, and had avoided Wyeth's monitoring systems (ie by the RBM) should itself be enough to find that a company as a whole had failed to maintain high standards.

Wyeth found no evidence that the evening meeting was an inducement to gain subsequent interviews with junior medical staff. Indeed, the evening meeting *followed* rather than preceded the lunchtime postgraduate meetings, and it was the postgraduate meetings which provided the opportunity for representatives to meet JHOs. There was no evidence that these long-standing, regular lunchtime meetings had been influenced in any way by an evening meeting such as the 28 October meeting. Wyeth did not accept that Clause 15.3 of the Code had been breached.

Wyeth found no evidence that its sales representatives wandered around local hospitals without prior appointment, and thus strongly refuted the allegation of a breach of Clause 15.4 of the Code. Wyeth representatives only met senior doctors if they had prior appointments, consistent with the policy for medical representatives issued by a local NHS trust.

Regarding the poster advertising the 28 October event, this was prepared by the JHO organiser. The Wyeth representative did not know about the poster prior to the meeting, and did not initiate, create or contribute to it in any way. The Zoton FasTab water-skier advertisement used by the JHO as the basis of the poster was taken from an old campaign no longer used by Wyeth. The Wyeth representative was first told about the poster by the JHO at the evening meeting on 28 October, by which time it had already been taken down (earlier on the same day). Wyeth double-checked to ensure that all such posters had been removed, and the JHO confirmed that this was the case. Wyeth therefore refuted a breach of Clause 20.1.

Finally, Wyeth found no evidence that its sales representative(s) had incorrectly stated that 'lansoprazole was number one on the formulary', and thus refuted the alleged breach of Clause 7.2. The representatives were informed verbally about the status of lansoprazole on the local formulary at local sales team meetings in May/June 2004, at which they were shown the open access hospital web pages from where they could download the formulary.

Wyeth confirmed that the representative had asked the JHO to invite doctors who had attended the lunchtime educational meetings; and on that basis the names of those who expressed interest in attending the dinner were collected. The representative did not know that the doctor would generate a poster (partly) for this purpose, and certainly was not involved in its creation. Indeed, as previously described, the representative did not know that the poster existed until after the start of the evening meeting on 28 October. Everyone who attended the evening meeting had attended a lunchtime educational meeting, despite the regrettable non-specific wording of the poster. In practice, this was probably not surprising, as most doctors had attended a lunchtime meeting, such that the probability of a doctor expressing an interest in the evening meeting of 28 October, who had not previously attended a lunchtime meeting, was low.

Wyeth confirmed that since March 2004 the representative in question had organised four restaurant meals involving doctors from the local hospital in addition to the 28 October meal. Two of these evening meals (22 April and 12 August) took place on the same day as a lunchtime educational meeting, and two (17 March and 26 October) took place within 12 days of a lunchtime meeting. All dinners therefore related to an educational meeting, with attendees at the evening meals having previously attended a lunchtime meeting, albeit this process was not adherent to Wyeth SOP 1.13, as previously described.

COMMENTS FROM THE COMPLAINANT ON PART OF WYETH'S RESPONSE

The complainant commented on Wyeth's response to the allegations that representatives wandered round hospitals without appointments in breach of trust policy and comments made by representatives about the status of lansoprazole in the formulary.

The complainant was aware of a number of situations where Wyeth representatives simply popped into clinical areas of a local hospital with the expectation of bumping into junior medical staff. Wyeth had casually dismissed the complaint, and gave no indication of how it believed the representatives approached junior medical staff. What level of 'evidence' was Wyeth seeking in relation to this? Video surveillance or similar would seem inappropriate and unreasonable.

There was confusion amongst junior medical staff at the local hospital about the local formulary recommendations. A number had independently said that Wyeth representatives had given the impression that lansoprazole was the formulary proton pump inhibitor recommendation. Junior doctors usually trusted that information given by the pharmaceutical industry was honest and accurate. Regardless of what had actually been said, the impression given by Wyeth representatives was inaccurate and misleading. Wyeth stated that 'representatives were informed verbally about the status of lansoprazole on the local formulary…in May/June 2004'. The complainant suggested that perhaps specific training on the local formulary might prove more useful to the representatives than an isolated conversation on the topic, and minimise the possibility that they might continue to (inadvertently) mislead.

PANEL RULING

The Panel noted that Clause 19.1 of the Code permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings, scientific congresses and other such meetings. Hospitality must

be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion. The costs involved should not exceed those which participants might normally pay when paying for themselves. The supplementary information to Clause 19.1 stated that it should be the programme that attracted delegates and not the associated hospitality or venue. The impression created by the arrangements was an important factor. Meetings organised for health professionals and/or administrative staff which were wholly or mainly of a social or sporting nature were unacceptable.

The Panel noted Wyeth's submission that the meeting was organised by a representative acting outside of the company's SOP. The Panel noted that nonetheless Clause 15.10 provided that companies were responsible for the activities of their representatives if these were within the scope of their employment even if contrary to instructions given.

The Panel noted that the Wyeth representative provided dinner in a restaurant on 28 October to 14 health professionals. There was no educational content, the evening was a social function held in a public restaurant and was advertised on this basis. This was totally unacceptable. It was seen as a social function by the doctor organising the meeting. The poster advertising the event made no reference to any educational content. A breach of Clause 19.1 of the Code was ruled.

The Panel considered that the representative had failed to maintain a high standard of ethical conduct; she had not followed the company's SOP nor had she complied with all the relevant requirements of the Code. A breach of Clause 15.2 was ruled. Although Wyeth had demonstrated that the representative had been trained the events were so clearly in breach of the Code that the Panel considered that the company had not maintained a high standard. A breach of Clause 9.1 was ruled. The Panel considered that the arrangements brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 of the Code was ruled.

The Panel noted that in addition to the meal at issue the representative had organised four other restaurant meals for doctors from the local hospital. All of these meals had been separated from educational meetings, two were held the same day as a lunchtime meeting and two were held within 12 days of a lunchtime meeting. These arrangements were wholly unacceptable. Provision of hospitality could not be delayed. Appropriate hospitality could be provided in association with meetings but it could not be provided later that day or even some days later. An educational meeting and a meal separated in time would be viewed as two different events. The Panel was concerned at the pattern of behaviour and that this appeared not to have come to Wyeth's attention until it had investigated the complaint.

With regard to the poster advertising the dinner and drinks, the Panel noted that the representative had first learned about its existence at the dinner on 28 October. The Panel noted that the dinner was informally organised by one of the JHOs at the request of the representative. Although the representative had thus delegated responsibility for some of the organization of the meeting to the JHO, the representative nonetheless remained responsible for it. Companies could not delegate their responsibilities under the Code to third parties. The poster incorporated an advertisement for ZotonFastab the display of which in a public area meant that a prescription only medicine had been promoted to the public. Thus the Panel ruled a breach of Clause 20.1 of the Code.

With regard to the other allegations the Panel noted that the parties' accounts differed; it was difficult in such cases to know exactly what had transpired. A judgement had to be made on the available evidence bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint.

With regard to the alleged use of the social functions to gain interviews with the junior medical staff the Panel noted that there was no evidence in this regard. It was thus difficult to determine where the truth lay. The provision of the hospitality might make the junior medical staff more likely to see the Wyeth representative. The social functions had been ruled in breach of the Code. There was no evidence in relation to Clause 15.3 of the Code thus the Panel had no option other than to rule no breach of Clause 15.3 of the Code.

With regard to the allegation that sales representatives wandered around the hospital in the expectation of meeting with hospital staff without prior appointment, the Panel noted that no specific dates or names of hospital staff had been provided. If such events occurred this would be outside hospital policy. The Panel noted that the allegation was denied by Wyeth. The Panel considered it had no option other than to rule no breach of Clause 15.4 of the Code.

The Panel considered it would be extremely helpful if Wyeth reinforced with all its representatives the need to comply with local arrangements when seeking appointments.

With regard to the allegation that some medical staff had the impression from Wyeth representatives that lansoprazole not omeprazole was the formulary choice, Wyeth had verbally informed representatives about the formulary choice in May/June 2004 and they were shown the open access hospital web pages from which they could download the formulary.

The Panel queried, given the confusion, whether it was sufficient to verbally instruct representatives about the local formulary. It would have been helpful if the representatives had been given details of the formulary and clear written instruction as to what could be said about lansoprazole in relation to it. The Panel considered it was curious that the number of lansoprazole prescriptions had increased despite the formulary. Nonetheless the Panel considered that it had no option other than to rule no breach of Clause 7.2 of the Code.

Complaint received **5 November 2004**

Case completed **4 February 2005**

NOVO NORDISK/DIRECTOR v SANOFI-AVENTIS

Alleged breach of undertaking

Novo Nordisk complained that a leavepiece for Lantus (insulin glargine) which had been ruled in breach of the Code had subsequently been displayed on a Sanofi-Aventis exhibition stand at a conference.

As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.

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 the industry that companies complied with undertakings.

The Panel noted that Novo Nordisk alleged that a leavepiece ruled in breach of the Code (Case AUTH/1593/6/04) and withdrawn in August 2004 had been displayed at a meeting in October. Sanofi-Aventis denied that the material had been displayed on its stand. Novo Nordisk provided photographs of Sanofi-Aventis' stand and stated that it had rearranged the leavepiece on the stand before it took the photograph.

The Panel was very concerned about the case. One of the parties was not providing accurate information. There was no way of determining on the balance of probabilities whether the material was present on the stand and how it had come to be there. The parties' accounts differed. It was impossible to determine where the truth lay. The Panel had no option other than to rule no breaches of the Code.

Novo Nordisk Limited complained that a leavepiece (ref LAN 3420703) for Lantus (insulin glargine) which had previously been ruled in breach of the Code had been displayed on a Sanofi-Aventis stand at a conference in October 2004.

As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.

COMPLAINT

Novo Nordisk stated that exhibition space at the conference was made available to pharmaceutical companies sponsoring the event. A Lantus leavepiece entitled 'Where next for patients with poor glycaemic control on pre-mixed insulins?' was displayed on the Sanofi-Aventis stand despite having been previously ruled in breach of the Code (Case AUTH/1593/6/04).

As Sanofi-Aventis had not appealed the ruling in Case AUTH/1593/6/04, it should have withdrawn the leavepiece. Failure to withdraw the leavepiece when it was knowingly in breach of the Code brought discredit upon, and reduced confidence, in the pharmaceutical industry in breach of Clause 2.

Novo Nordisk provided the leavepiece picked up at the Sanofi-Aventis exhibition stand, along with photographs that showed it was present at the stand.

When writing to Sanofi-Aventis, the Authority asked it to respond in relation to Clauses 9.1 and 22 of the Code as well as Clause 2.

RESPONSE

Sanofi-Aventis denied any wrong doing on its part with regard to the withdrawal of the leavepiece in question. The company also rejected any assertion that its representative who attended the first day of the two day meeting either wilfully or accidentally used the leavepiece and/or displayed it on the promotional stand.

With regard to the withdrawal of the leavepiece, Sanofi-Aventis stated that the company's standard operating procedure (SOP) 'Withdrawal of Material' had been followed. On 20 August all staff in the diabetes division were told in writing to stop using the leavepiece and several other items and what to do with any copies that they had left. A senior medical advisor and the diabetes marketing manager signed this letter.

On Monday 29 November, two directors of Aventis interviewed the regional sales manager, the representative and the hospital representative responsible for the conduct of the meeting in question. As a result of these in depth interviews Sanofi-Aventis was confident that the regional sales manager acted in accordance with the principles set out in the SOP. He promptly informed his sales team to stop using the leavepiece and to return all of their copies to him for onward transmission to Aventis for destruction. He received approximately 40-50 copies from his team. The regional sales manager clearly recalled that he received documents for each member of his team because he had had to send out a reminder to some members of his team about a different promotional item that the company had stopped using and he was pleased at the prompt and complete response from his team on this other occasion.

The regional sales manager recorded the leavepieces that were returned to him on a list that was enclosed with the bundle of documents that were returned to head office for destruction. Regrettably, he did not keep a duplicate of the list and head office did not have a copy of it either. Sanofi-Aventis recognised this as a weakness in the system and planned to change it. Notwithstanding the absence of a copy of this list, Sanofi-Aventis was confident in the staff's recollection of events and saw no reason to question the truth of their recollections further.

Following Novo Nordisk's complaint, the regional sales manager made an unheralded check of all promotional materials kept by the representative and did not find any that were out-of-date.

Sanofi-Aventis denied any breach of the Code with respect to the appropriateness and completeness of

the actions taken by the company to inform staff appropriately and remove the leavepiece from use.

The representative was adamant that she did not have any of copies of the leavepiece in her possession and therefore could not have used them at the meeting as alleged. Even given the extremely unlikely proposition that she had a rogue copy of the leavepiece, Sanofi-Aventis contended that she would not have dressed a promotional table with a single clock, a video cassette and a leavepiece propped up in the almost ridiculous manner as shown in the photographs submitted by Novo Nordisk. The spartan Sanofi-Aventis stand was in stark contrast to another company's table in the right foreground, which was fully laden with promotional materials. Sanofi-Aventis contended that the scene as photographed was not a credible representation of reality and gave every impression of having been staged.

Sanofi-Aventis noted that it was daylight outside making the time sometime before 5.30pm, when the workshop sessions of the meeting would still have been in progress. Curiously, there were no people in the photograph when one would have expected many delegates and company personnel to be present. Sanofi-Aventis considered that it would have been sensible if this were a real event, for the photographer to include an independent person in the frame to make it clear that the scene could not be interpreted as staged because they clearly had the intention of illustrating a misdemeanour.

Sanofi-Aventis stated that the representative had packed up the stand and left the meeting before 3.30pm. The stand was left up for a colleague to take over the following day.

In the poor quality copies of the photographs that Sanofi-Aventis had been provided with, it appeared that there was a person in the left foreground of one of the pictures. The evidence of this person might well be material if they could be traced. Sanofi-Aventis was currently trying to contact other pharmaceutical company representatives, as well as delegates at the meeting to ascertain their recollections of the meeting. Sanofi-Aventis wondered if Novo Nordisk had any independent witness evidence that would support its assertions.

It would be interesting, but Sanofi-Aventis accepted not confirmatory, to enlarge the photograph in order to see what time it was on the clock. Of course Sanofi-Aventis accepted that the clock might not be accurate nor did the representative have to be present at the time that the photographs were taken for a breach of the Code to be ruled.

Notwithstanding the above, it was clear that the representative left the meeting early because she was not staying for the second day. There was, therefore, a distinct possibility that someone might have placed a copy of the withdrawn item in the prominent and frankly ridiculous position in which it had been photographed.

Sanofi-Aventis concluded from the reported facts and the photograph submitted by Novo Nordisk that someone had acted mischievously, if not maliciously. The possibility that this was a simple misunderstanding between the parties involved was untenable. This was an extremely serious case and a career-limiting event for the person, or persons responsible for any deceit.

After carefully interviewing the representative twice, first by her direct line manager and the diabetes marketing manager, and then by two directors, Sanofi-Aventis was satisfied that she was neither mistaken, nor was she wilfully misleading the company when she stated that she did not use the leavepiece at the meeting.

The facts as reported by the representative

The representative only attended the first day of the meeting because she was covering for a colleague who only returned from holiday that day. The colleague, a hospital representative, attended the second day of the meeting. It had been agreed that the first representative would erect the stand and use her stock of promotional materials on the first day and leave the table and stand up for the hospital representative to use with her own stock of materials on the next day. This was done because other pharmaceutical companies were also at the meeting and the representatives wanted to ensure that they maintained the same location for the stand. There were two rooms available for commercial stands at the meeting; Sanofi-Aventis shared the larger of the two with three other companies, and two companies were in the other room.

The representative arrived at the meeting on the morning of the first day at about 9am in time to set up the stand before the start of the meeting. The representative dressed the table with: treatment algorithm leavepieces; treat to target promotional pieces; patient information leaflets; videos explaining the use of the insulin delivery pen device for patients; diabetes text books; promotional aids; insulin pouches and insulin demonstration delivery device pens with placebo water cartridges.

There were 60-70 delegates at the meeting. The representative stayed with her stand all of the time that she was at the meeting apart from two, or possibly three brief occasions.

The representative stated that she packed up the table and left the stand on it at approximately 3.30pm. She left a box of demonstration pens and water cartridges under the table for the hospital representative to use the next day as well as two or three patient videos. Importantly, she left a small sheaf of treatment algorithms on the table that she thought some of the delegates who she had not already seen might find useful together with a clock that she did not have room for and thought that some doctor might find it a useful practice aid. Sanofi-Aventis noted that the literature that the representative was using at the time was A4 sheet documents or smaller; not three composite A4 sheet gatefold pieces such as the withdrawn leavepiece at issue. The representative was adamant that there could be no confusion, or possibility that she left a gatefold piece on the stand when she cleared up the table.

The Novo Nordisk representative was still in the room when the Sanofi-Aventis representative left. The Sanofi-Aventis representative was not sure if the Novo Nordisk representative's manager/colleagues were still there.

The representative in question had worked for Aventis for almost a year. Prior to this she worked as a sales representative for three years with another pharmaceutical company. The representative had passed her ABPI examination. Her manager had been on one field visit with her since 20 August, the date when the leavepiece was withdrawn, and did not see any indication that the representative was still in possession of, or referring to it. The manager spontaneously reported that the representative was diligent and very good at the administrative tasks associated with her job and was a first-class representative and member of his team.

Evidence from the hospital representative

The hospital representative arrived at the meeting venue before 10am on the second day of the meeting. She only recalled finding on or under the stand when she arrived, a box of demonstration insulin delivery pens with placebo water cartridges, a couple of plastic carrier bags and a meeting delegate pack. The delegate pack was given out by the organisers and importantly contained a list of the delegates. All of these items were under the table, hidden by the tablecloth. There was no clock and no other literature. The hospital representative dressed the stand with her own materials.

The hospital representative clearly remembered saying good morning to the Novo Nordisk representative because the Novo Nordisk representative deliberately blanked her which was very unusual as they had known each other for several years. The hospital representative recalled that the Novo Nordisk representative did not stay on her stand all day, but could not remember precisely when she left.

Summary

What was clear in this case was that there were marked differences between the complainant's view of the matter and the Sanofi-Aventis view. These differences could not be considered to be simple misunderstandings. The photographic evidence submitted by Novo Nordisk looked out of keeping with the way that a trained and experienced representative would dress a promotional stand. It was known that on the first day the representative left before the meeting ended while there was still good daylight, as shown in the photographs. She left her tablecloth and stand up for the hospital representative to use the following day.

The representative was trusted and well-respected and had had every opportunity to admit any errors or shortcomings about the use of the leavepiece without pressure of any further consequence. The representative was adamant that she neither had a copy of the leavepiece, nor did she leave a copy of it on the stand. This assertion by the representative, coupled with the report from her manager that he received copies of the leavepiece from her and all of his team for destruction by head office, his praise of the representative's attention to administrative detail and the face-to-face interviews held by two Sanofi-Aventis directors led Sanofi-Aventis to conclude that its management of material withdrawal in general, and the activities of its representative and her colleagues did not constitute a breach of Clauses 2, 9.1 or 22. The company denied any wrongdoing whatsoever in this case.

The Panel decided to send Sanofi-Aventis' response to Novo Nordisk for comment.

FURTHER COMMENTS FROM NOVO NORDISK

Novo Nordisk read Aventis' response with great concern. In essence, Sanofi-Aventis denied any breach of the Code and seemed to allege that Novo Nordisk had deliberately planted a copy of the leavepiece on the unmanned Sanofi-Aventis stand and taken a photograph of it. This was an extremely serious allegation.

All Novo Nordisk personnel who attended the meeting, the diabetes marketing director, the regional sales manager and the representative, were interviewed for their recollection of events. The marketing manager was also interviewed as he received the call from the diabetes marketing director that afternoon concerning the matter.

The regional sales manager remembered the Sanofi-Aventis representative leaving the stand around the end of the afternoon coffee break, at approximately 3.30pm and this was in agreement with the Aventis representative's recollection. When the delegates returned to the meeting after coffee, leaving the room empty, save for the representatives manning the various stands, the regional sales manager looked at the materials which had been left out on the Sanofi-Aventis stand. He clearly recalled two separate piles of materials with an estimated 10 pieces in each as well as blood glucose monitoring diaries which were not mentioned by Sanofi-Aventis. He took one piece from each of the two piles and asked the diabetes marketing director if they ought to have been withdrawn. The diabetes marketing director suspected that one of the items had been ruled in breach and telephoned head office immediately to check. He spoke to the marketing manager giving the reference codes for the two pieces. The marketing manager remembered receiving the call and on confirming that the leavepiece should have been withdrawn by Sanofi-Aventis, within ten minutes he telephoned the Novo Nordisk representative to inform her of this. The regional sales manager took a photograph of the leavepiece as proof that Sanofi-Aventis had not withdrawn all of its materials as it had undertaken so to do.

The digital camera used was very discrete and although there were other companies' representatives still present at the time, around 4pm, the regional sales manager was careful not to draw attention to his actions. However he stood the leavepiece up and opened it out on the stand in order to better identify it in the picture, bearing in mind that many materials could look similar from the front as was the case with the Sanofi-Aventis leavepieces which had similar visuals.

In summary, it was quite clear that the leavepiece in question was present on the stand for whatever reason, placed there by the local representative. To suggest that a director of Novo Nordisk would collude in some sort of deception with other colleagues was outrageous. Similarly this implication

called into question the character of the sales manager, marketing manager and the representative.

The Panel decided to send Novo Nordisk's response to Sanofi-Aventis for comment.

FURTHER COMMENTS FROM SANOFI-AVENTIS

Sanofi-Aventis stated that it reconsidered this case in the light of Novo Nordisk's further comments. The representative was re-interviewed by directors of Sanofi-Aventis and the further evidence submitted by Novo Nordisk was reviewed in detail. The conclusions reached following this review remained the same as before. Sanofi-Aventis denied that the representative 'used and displayed' the previously withdrawn leavepiece at the meeting in question.

The reasons for this position were:

a) The representative confirmed she did not leave any materials of the sort described by Novo Nordisk on the Sanofi-Aventis stand and that was supported by other evidence.

It was alleged that 'two separate piles of materials with an estimated ten pieces in each as well as blood glucose monitoring diaries' that were 'left out on the Sanofi-Aventis stand'.

The representative recollected taking certain items to the meeting to use on the promotional stand and a list of these items was provided. However, she could not have taken the leavepiece to the meeting. The representative had joined the Lantus team only in March 2004 and did not order multiple copies of the leavepiece. She received a small number of samples during her initial product training in March 2004 and returned these copies to her manager following the notification of its withdrawal from head office in August 2004.

In addition, aware of a background of complaints made by Novo Nordisk, the representative was very careful not to leave any major promotional materials on the table when she left. She took any promotional items, ie those containing product claims, away with her and locked them in her car boot. She did not specifically recall leaving blood glucose monitoring diaries on the table. However, she conceded that she might have done so.

When she left the meeting at approximately 3.30pm she recalled leaving a clock, a number of treatment algorithms, insulin pouches and a small number of video cassettes on the table. In addition, she left a number of insulin pens behind the stand.

b) The evidence submitted by Novo Nordisk was not of itself conclusive and Novo Nordisk must provide further independent evidence.

Photographic evidence of itself was not conclusive and must be supported by objective and independent evidence. To highlight the risk of relying solely on photographic evidence, Novo Nordisk admitted that the alleged material was moved for the purposes of the photograph.

In the light of the allegations made by Novo Nordisk and of the fact that the only evidence submitted was photographic, Sanofi-Aventis requested that Novo Nordisk answered the following questions which might assist the Panel in elucidating the facts of this case:

1 Was there evidence that the leavepiece was used for promotional purposes with health professionals by the representative at the meeting? Was Novo Nordisk able to provide evidence to show that the leavepiece was 'used and displayed' when health professionals were present?

2 Digital cameras provided a 'date and time' footprint. Sanofi-Aventis asked Novo Nordisk to provide access to all the original photographs with this important information included, and to confirm the date and time of the photographs and where the photographer stood.

3 Why did Novo Nordisk not contact Sanofi-Aventis as soon as it became aware that the leavepiece was apparently present on the stand to ask for an explanation? This was clearly possible at 4pm on a Friday.

4 Did Novo Nordisk know what happened to the remaining items from the 'two piles of materials' as they were not present when the hospital representative arrived on the second day of the meeting? Was the material alleged to have been found being held with the Authority?

5 What were the local weather conditions on the day(s) on which the photographs were taken?

Sanofi-Aventis believed it was essential that Novo Nordisk provided this further information.

In conclusion, Sanofi-Aventis submitted that the leavepiece at issue was properly withdrawn, and denied that it was 'used and displayed' and therefore denied breaches of Clauses 2, 9.1 and 22.

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 the industry that companies complied with undertakings.

The Panel noted that Novo Nordisk alleged that a leavepiece ruled in breach of the Code (Case AUTH/1593/6/04) and withdrawn in August 2004 had been displayed at a meeting in October. Sanofi-Aventis denied that the material had been displayed on its stand. Photographs had been supplied by Novo Nordisk and the company had stated that the leavepiece had been stood up and opened out for the photograph.

The Panel was very concerned about the case. One of the parties was not providing accurate information. There was no way of determining on the balance of probabilities whether the material was present on the stand and how it had come to be there. The parties' accounts differed. It was impossible to determine where the truth lay.

The Panel had no option other than to rule no breach of Clauses 2, 9.1 and 22 of the Code.

Complaint received **10 November 2004**

Case completed **14 March 2005**

PRESCRIBING ADVISER v SANKYO

Promotion of Olmetec

A prescribing adviser at a primary care trust (PCT) complained on behalf of two local PCTs and a local NHS trust formulary working group about two letters sent by Sankyo to local general practitioners. The letters referred to the inclusion of Olmetec (olmesartan) in the local formulary. Neither the local PCTs nor the formulary working group had asked for the letters to be sent or authorized their dispatch. The complainant alleged that the letters were disguised promotion.

The Panel noted that the first letter was headed 'Recent formulary inclusion: Olmetec'. The three page letter discussed, *inter alia*, the efficacy, tolerability and cost of Olmetec. The letter was imprecise as to which local formulary now included Olmetec. The second letter headed 'Re: Recent formulary inclusion: Olmetec' clarified the situation.

The Panel noted that the PCTs and formulary working group represented by the complainant had neither requested nor authorized the despatch of the letters. The Panel considered, however, that companies could refer to the inclusion of their products in formularies and suchlike in promotional material but any such reference had to comply with the Code.

The Panel considered that from its content and appearance the first letter was clearly promotional material for Olmetec. There was no suggestion that it had been sent at the direction of or on behalf of the local PCTs or formulary working group. It was not disguised in that regard. No breach of the Code was ruled.

The Panel noted Sankyo's submission that the second letter was not promotional; it had been sent to clarify a point made in the first letter. The Panel considered, however, that stating which formulary included Olmetec was a claim for the product and in any event informing general practitioners that a product was included in their local formulary would promote the prescription of that product. The second letter was thus promotional for Olmetec but the Panel did not consider that its content was disguised as alleged. There was no implication that the letter had been sent on behalf of the formulary working group. No breach of the Code was ruled.

A prescribing adviser at a primary care trust (PCT) complained on behalf of two local PCTs and a local NHS trust formulary working group about two letters (refs OLM 100.1 and OLM 115.1) each sent by Sankyo Pharma UK Ltd to 143 local general practitioners. The letters referred to the inclusion of Olmetec (olmesartan) in a local formulary.

COMPLAINT

The complainant stated that the two letters related to the inclusion of Olmetec in the health-economy wide joint formulary.

The joint PCTs and NHS trust formulary working group neither requested the company to send these letters, nor authorised it to do so, and was of the opinion that they contravened Clause 10 of the Code.

When writing to Sankyo the Authority asked it to respond in relation to Clause 10.1 of the Code.

RESPONSE

Sankyo stated that the first letter (ref OLM 100.1) was sent in June and was an approved promotional letter and as such carried prescribing information. This letter was sent as the result of requests received by Sankyo's sales force that there was a lack of clarity in the area about the addition of Olmetec to the local formulary six months after being accepted by the trust.

As a result of an enquiry received by Sankyo about the first letter as to exactly which PCTs included Olmetec on their formularies, the company considered that a further letter of clarification was warranted as it noticed in hindsight that the first letter was not prescriptive enough as it did not list the specific PCTs in question.

The second letter, sent in September to the same doctors, was a factual and professional clarification from Sankyo's medical director and stated precisely on which local formulary Olmetec was available. It mentioned the product but not the indication or any promotional claims. The purpose of the letter was clearly stated in the content; it was therefore not considered to be a promotional piece as defined by the Code as it was a letter of clarification.

Sankyo agreed that the first letter was intended to be promotional while at the same time informing doctors of the addition of Olmetec to the local formulary. This was not produced for or on behalf of the PCT and therefore did not, in Sankyo's opinion, require its approval as it was simply re-confirming a decision that had been made in October 2003 by the local NHS trust. Furthermore, the letter was produced 6 months after adoption onto the formulary. This letter was not in breach of Clause 10.1 as disguised promotion as it was clearly a promotional letter. The second letter was sent on a professional basis from Sankyo's medical director as opposed to any sales or marketing involvement; it was sent simply for clarification after a request had been received from a customer in response to Sankyo's original promotional letter.

The nature of the factual content and its purpose to issue a corrective statement led Sankyo to consider that it was not in breach of Clause 10.1 as it was not intended to be promotional in its content either by overt content or by disguise.

PANEL RULING

The Panel noted that the first letter was headed 'Recent formulary inclusion: Olmetec' and began 'I am writing to inform you of a new addition to the formulary. A new treatment for Essential Hypertension has recently been added to the [name]'.

The three page letter discussed Olmetec in relation to its efficacy, tolerability and cost and featured a cost comparison of Olmetec with the most prescribed (by cash spend) angiotensin II receptor antagonists in the region in 2003. The letter concluded by stating that the author looked forward to discussing Olmetec with the recipient. The second letter was signed by the medical director and was headed 'Re: Recent formulary inclusion: Olmetec' and referred to the first letter regarding the formulary status of Olmetec. It identified the formulary on which the product was included and referred the reader to the company's medical services team if they had any queries.

The Panel noted that Sankyo had provided a copy of a letter from a consultant physician and clinical director of acute medicine at the NHS trust which stated that 'Olmesartan is now in our Trust formulary … our formulary is an interface formulary covering [a named hospital] and the associated PCTs'. This letter did not refer to the dissemination by the company of the information therein or to the letters, subject to the present complaint.

The Panel noted the submission that the PCTs and formulary working group represented by the complainant had neither requested nor authorised the despatch of letters and the subsequent allegation of a breach of Clause 10. The Panel considered, however, that companies could refer to the inclusion of their products in formularies and suchlike in promotional material but any such reference had to comply with the Code.

The Panel considered that the content and appearance of the first letter at issue was such that it was clearly promotional material for Olmetec; it did not purport to be anything else. There was no suggestion that the provision of information about the product's recent inclusion on the local formulary was at the direction of or on behalf of the complainant's PCTs or formulary working group. It was not disguised in that regard. No breach of Clause 10.1 was ruled.

The Panel noted Sankyo's submission that the second letter was not promotional; it had been sent to clarify a point made in the first letter. The letter stated that '… Olmetec is available on [named] NHS trust formulary …'. In the Panel's view this was a claim for Olmetec. In that regard the Panel noted that the supplementary information to Clause 7, Information, Claims and Comparisons, stated that the application of that clause was not limited to information or claims of a medical or scientific nature. It included, *inter alia*, information or claims relating to pricing and market share. In any event the Panel considered that informing general practitioners that a product was included in their local formulary would promote the prescription of that product. The Panel thus considered that the second letter was promotional for Olmetec. As with the first letter considered above, however, the Panel did not consider that the content of the second was disguised as alleged. There was no implication that the letter had been sent on behalf of the formulary working group. No breach of Clause 10.1 was ruled.

Complaint received **16 November 2004**

Case completed **18 January 2005**

CASE AUTH/1654/11/04

HEALTH BOARD PRESCRIBING ADVISOR v PFIZER

Cardura XL leavepiece

The prescribing advisor to a health board complained about the promotion of Cardura XL (modified release doxazosin) by Pfizer.

A leavepiece stated:

'Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin:

- **Lower risk of postural hypotension**
- **No need for dose titration …**
- **Fewer patient consultations**
- **Better compliance**
- **Better achievement of BP targets'.**

The complainant was concerned that four of the bullet points 'Lower risk of postural hypotension', 'Fewer patient consultations', 'Better compliance' and 'Better achievement of BP targets' could not be made from the references cited. Gotzen (1998) and Chung *et al* (1999) were cited as showing lower risk of postural hypotension. Gotzen looked at postural hypotension after the medicine was stopped for two days and then restarted, rather than looking at patients on continuous therapy. Chung *et al* stated 'There was no obvious difference in the type and incidence of specific adverse events between the two treatments' and went on to state 'In conclusion, the improved absorption profile of [Cardura XL] will likely minimise the risk of unintended adverse hypotensive effects'.

It was alleged that the claim about fewer patient consultations was not substantiated by Os *et al* (1999) which stated 'It might be expected, therefore, that the simplified dosing regimen with [Cardura XL] will likely result in the need for fewer office visits among hypertensive patients prescribed this formulation'.

The complainant could not find any details in Gotzen looking at patient compliance.

Anegón *et al* (2002) was cited in support of the claim about the better achievement of BP targets. However, as the authors acknowledged, 'The design of the study did not allow comparison of the two formulations regarding effectiveness or tolerability'.

Anegón *et al* was also cited in support of the claim 'No need for dose titration'. However, in this study patients were already prescribed doxazosin conventional release and simply switched to the modified release formulation at one of the visits. The complainant failed to see how this paper could be cited as a reference for this claim although she accepted that it could be substantiated by others.

The Panel noted that the four claims at issue were preceded by the statement 'Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin:'. The Panel considered that to state that something was *likely* to happen rarely negated the impression that something would happen. The material in question thus implied that, compared with taking standard doxazosin, patients taking Cardura XL had been proven to have a lower risk of postural hypotension, required fewer consultations and be more compliant with therapy, and needed to be substantiated on that basis. The Panel noted that in each case Pfizer had relied on its claims being qualified by the word 'likely'. With regard to the claim 'Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin …. Better achievement of BP targets' the Panel noted that Pfizer had acknowledged that it needed to be put into context. The Panel thus considered that the claims were misleading and had not been substantiated. Breaches of the Code were ruled.

The final claim at issue read, in full, 'Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin: … No need for dose titration – therapy can be started at the effective therapeutic dose of 4mg once daily' and was referred to Chung *et al*, Os *et al* and Anegón *et al*. In the Panel's view most readers would assume that the claim meant that when initiating doxazosin therapy with Cardura XL, there was no need to titrate the dose. Anegón *et al*, however, evaluated the tolerability and effectiveness of replacing standard doxazosin with Cardura XL; no patient had doxazosin therapy initiated with Cardura XL. The Panel thus did not consider that Anegón *et al* substantiated the claim 'No need for dose titration – *therapy can be started* at the effective therapeutic dose of 4mg once daily' (emphasis added). The Panel considered that although the claim could be substantiated by other material including the summary of product characteristics (SPC), it was misleading to cite Anegón *et al* in support of it. A breach of the Code was ruled in this regard. As the claim could be substantiated by other material the Panel ruled no breach of the Code in that respect.

The prescribing advisor to a health board complained about the promotion of Cardura XL (modified release doxazosin) by Pfizer Limited. The complainant submitted two A4 cards, one headed 'Cardura XL effective treatment of hypertension with less risk of postural hypertension than standard doxazosin' (ref CAR 687r) and the other 'Important information on doxazosin' (ref CAR 689r).

COMPLAINT

The complainant was particularly concerned about five claims made about Cardura XL in relation to conventional release doxazosin. The claims, which appeared as bullet points on the card headed 'Cardura XL effective treatment of hypertension with less risk of postural hypotension than standard doxazosin', were:

* 'Lower risk of postural hypotension' (referenced to Gotzen 1998 and Chung *et al* 1999)

'No need for dose titration …'

* 'Fewer patient consultations' (referenced to Os *et al* 1999)
* 'Better compliance' (referenced to Gotzen)
* 'Better achievement of BP targets' (referenced to Anegón *et al* 2002)

The complainant alleged that the four claims which she had asterisked could not be made from the references cited. Gotzen and Chung *et al* were cited as showing lower risk of postural hypotension. This might have been the case in Chung *et al* within the small numbers of patients studied. However Gotzen looked at postural hypotension after the medicine was stopped for two days and then restarted, rather than looking at patients on continuous therapy. Chung *et al* stated 'There was no obvious difference in the type and incidence of specific adverse events between the two treatments' and went on to state 'In conclusion, the improved absorption profile of [Cardura XL] will likely minimise the risk of unintended adverse hypotensive effects'.

The complainant alleged that the claim about fewer patient consultations was not substantiated by Os *et al*. The paper stated 'It might be expected, therefore, that the simplified dosing regimen with [Cardura XL] will likely result in the need for fewer office visits among hypertensive patients prescribed this formulation'.

The complainant could not find any details in Gotzen specifically looking at patient compliance. Differences between the two formulations of doxazosin in relation to patient compliance were not reported.

Anegón *et al* was cited in support of the claim about the better achievement of BP targets. However, as the authors acknowledged, 'The design of the study did not allow comparison of the two formulations regarding effectiveness or tolerability'. The study involved hypertensive patients with two phases – the initial phase involved the use of a conventional formulation of doxazosin and the second phase involved the use of modified release doxazosin. The two formulations were not compared directly with each other. The authors concluded 'Doxazosin in the standard formulation was effective and well tolerated for the purpose of decreasing BP….'.

Anegón *et al* was also cited in support of the claim 'No need for dose titration'. However, in this study patients were already prescribed doxazosin conventional release and simply switched to the modified release formulation at one of the visits. The complainant failed to see how this paper could be cited as a reference for this claim although she accepted that it could be substantiated by others.

When writing to Pfizer, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

Pfizer considered that the claims could be justified and did not breach the Code. However, as part of a continuing Cardura XL campaign development, the leavepiece in question had been removed from circulation.

Pfizer noted that the five bullet points at issue were preceded by the statement 'Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin:'. The claims, in full, thus read:

'Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin: … Lower risk of postural hypotension'

Chung *et al* provided the pharmacokinetic rationale for an improved tolerability profile of Cardura XL compared with doxazosin immediate release. Pfizer believed the evidence was represented in a balanced manner by its use of the word 'likely' within the claim.

Gotzen reported that 'Apart from palpitations, all other symptoms of orthostatic hypotension were reported significantly more frequently with standard doxazosin' and that 'renewed intake of doxazosin on the third day … resulted in significant differences in the orthostatic tolerance test … this difference was statistically significant'.

Pfizer noted the complainant's comment that the study evaluated the effects after a two-day interruption in therapy; however, in the treatment of hypertension the drop-out rate was high (cited as 30-50% in Gotzen) and therefore the chances of a patient taking a 'drug holiday' was high. Further, the clear difference in orthostatic hypotension symptoms was seen despite a difference in dosing – doxazosin immediate release was administered at 2mg/day and Cardura XL was administered at 4mg/day.

Again, Pfizer did not claim that Cardura XL would result in less postural hypotension, but was likely to result in a lower risk of postural hypotension.

Pfizer therefore believed that the claim was adequately substantiated from the cited publications.

'Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin: … Fewer patient consultations'

Pfizer noted that the complainant had alleged that this claim was not substantiated by Os *et al* as the paper stated 'It might be expected, therefore, that the simplified dosing regimen with [Cardura XL] will likely result in the need for fewer office visits among hypertensive patients prescribed this formulation'. Pfizer noted that it had used the word 'likely' in the claim and so it considered that, as written, the claim was adequately substantiated.

Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin: …. Better compliance.

Pfizer noted that the complainant had stated that there were no details in Gotzen specifically looking at patient compliance.

Gotzen acknowledged the difficulties of ensuring patient compliance when treating hypertension, quoting the estimated drop-out rate as 30-50%. Gotzen concluded 'a once daily dose of [Cardura XL] 4mg offers a safer and compliance-promoting alternative for antihypertensive therapy with alpha blockers'.

Pfizer submitted that it did not claim that Cardura XL would result in better compliance; however it was credible and reasonable to conclude that if better tolerability against immediate release doxazosin could be demonstrated, patient compliance was likely to be better.

Pfizer considered that the evidence adequately supported its claim by its use of the word 'likely' and also that the author's opinion was represented in a balanced manner.

'Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin: … Better achievement of BP targets'

[Cardura XL] obviated the need for titration through 1mg and 2mg doses, as was required by the summary of product characteristics (SPC) for immediate release doxazosin. Four milligrams was the therapeutically effective dose for both forms of doxazosin, but was the starting dose with Cardura XL. IMS data had shown that in patients prescribed immediate release doxazosin this was the least commonly prescribed dose while 1mg was the most commonly prescribed even though blood pressure was not controlled. Therefore by simplifying prescribing, Cardura XL was able to demonstrate better efficacy than immediate release doxazosin.

Pfizer accepted that within the leavepiece at issue, this claim would require to be put within context.

In response to a request for further information Pfizer noted that in the leavepiece the claim 'No need for dose titration' was referenced to Anegón *et al*. The Cardura XL SPC was the main supporting reference to this claim. The SPC stated that the starting dose of Cardura XL was 4mg, which was a therapeutically effective dose. Although Anegón *et al* evaluated a switch from standard doxazosin to Cardura XL, Pfizer submitted that it further supported its claim. Patients in the study were switched from standard doxazosin to Cardura XL at a starting dose of 4mg, irrespective of the dose reached with standard doxazosin. They were therefore initiated at 4mg of Cardura XL and did not need dose titration.

In conclusion Pfizer considered that the claim 'No need for dose titration' could be justified and did not breach the Code.

PANEL RULING

Panel noted that the four claims asterisked by the complainant had appeared on the leavepiece entitled 'Cardura' XL effective treatment of hypertension with less risk of postural hypertension than standard doxazosin'. The claims were preceded by the statement 'Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin:'. The Panel considered that to state that something was *likely* to happen rarely negated the impression that something would happen. The material in question thus implied that, compared with taking standard doxazosin, patients taking Cardura XL had been proven to have a lower risk of postural hypotension, require fewer consultations and be more compliant with therapy, and needed to be substantiated on that basis. The Panel noted that in each case Pfizer had relied on its claims being qualified by the word 'likely'. With regard to the claim 'Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin …. Better achievement of BP targets' the Panel noted that Pfizer had acknowledged that it needed to be put into context. The Panel thus considered that the claims were misleading and had not been substantiated. Breaches of Clauses 7.2 and 7.4 were ruled in respect of each claim.

The final claim at issue read, in full, 'Treatment with Cardura XL is therefore likely to bring you the following benefits over standard doxazosin: … No need for dose titration – therapy can be started at the effective therapeutic dose of 4mg once daily' and was referred to Chung *et al*, Os *et al* and Anegón *et al*. In the Panel's view most readers would assume that the claim meant that when initiating doxazosin therapy with Cardura XL, there was no need to titrate the dose. Anegón *et al*, however, evaluated the tolerability and effectiveness of *replacing* standard doxazosin with Cardura XL; no patient had doxazosin therapy initiated with Cardura XL. The Panel thus did not consider that Anegón *et al* substantiated the claim 'No need for dose titration – *therapy can be started* at the effective therapeutic dose of 4mg once daily' (emphasis added). The Panel considered that although though the claim could be substantiated by other material including the SPC, it was misleading to cite Anegón *et al* in support of it. A breach of Clause 7.2 was ruled. The Panel ruled no breach of Clause 7.4 of the Code as the claim could be substantiated.

The Panel noted that none of the claims at issue appeared on the card headed 'Important information on doxazosin'. Although one claim 'no titration is necessary' was closely similar to 'no need for dose titration' as considered above, it was not referenced to Anegón *et al* which was the issue at the heart of the complaint. The Panel did not consider it had received a complaint about the card headed 'Important information on doxazosin' and thus made no rulings in that regard.

Complaint received **22 November 2004**

Case completed **16 February 2005**

CASE AUTH/1655/11/04

PRACTICE PHARMACIST/DIRECTOR v WYETH

Switch programme and an alleged breach of undertaking

A practice pharmacist complained about a switch service offered by a representative from Wyeth. The complainant had advised the representative that the general practitioner practice was more interested in reviewing the dose of proton pump inhibitors (PPIs) than the choice of medicine. The representative had stated that she could engage the services of a third party, for which there would be no charge to the practice, to facilitate a change from Zoton capsules (lansoprazole) to Zoton FasTab. The complainant was concerned that Wyeth continued to offer support to practices for switching to a specific product further to a previous ruling of a breach of the Code, Case AUTH/1561/3/04. As the complaint involved a breach of undertaking it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings.

Wyeth submitted that the service to which this complaint related was part of a new service which the company developed further to Case AUTH/1561/3/04.

The Panel noted that the complainant had, *inter alia*, alleged a breach of the undertaking given by Wyeth in Case AUTH/1561/3/04 which concerned a switch programme whereby patients on Zoton capsules were switched to Zoton FasTab; breaches of the Code had been ruled.

The Panel considered that its ruling in a previous case, Case AUTH/1606/7/04, which considered whether arrangements for Wyeth's revised switch programme were in breach of the undertaking given in Case AUTH/1561/3/04, was relevant here.

In Case AUTH/1606/7/04 the Panel noted that there were differences between the switch programme at issue in Case AUTH/1561/3/04 and the service at issue in the present case, Case AUTH/1606/7/04; the revised service was not restricted to a switch from Zoton capsules to Zoton FasTab but was available for any oral PPI of the doctor's choice. The Panel noted Wyeth's submission that the prescribing decision of the GP had to be made in writing in advance of the offer of the service. The medication review booklet explained that the Gastrocare service was available to review any oral PPI dose at the request of the practice. The representatives' 'Action plan: Gastrocare service offerings' explained that if the GP chose to change from one formulation of a PPI medication to another in a dose for dose switch, the most suitable service was the GP System Specialist Implementation. If any other change was required, or if the GP did not wish for this service, the GP was offered the Gastrocare audit review. The Panel considered that the service at issue was sufficiently different from that considered in Case AUTH/1561/3/04; the service was no longer restricted to switches from Zoton capsules to Zoton FasTab but was available for all oral PPIs. The Panel considered there was no breach of the undertaking previously given. The Panel had therefore ruled no breaches of the Code.

Turning to the present case, Case AUTH/1655/11/04, in relation to the alleged breach of undertaking the Panel noted Wyeth's submission that the material and service offering at issue in the present case were the same as those considered in Case AUTH/1606/7/04. The Panel thus considered that its ruling in Case AUTH/1606/7/04 applied here. No breaches of the Code were thus ruled.

In relation to the allegations about the conduct of the representative, the Panel noted that a previous case, Case AUTH/1652/11/04, considered the role of the representative and the revised service.

In Case AUTH/1652/11/04 the Panel did not consider that the arrangements for the promotion of Zoton FasTab and the offer of the revised service by the representative were sufficiently separate. The discussion about Zoton FasTab concluded with a discussion about switching patients to it. The Panel considered that the subsequent introduction of a switch service by the representative would not be seen as sufficiently separate to the promotional discussions about switching to Zoton FasTab that immediately preceded it. The introduction of the service and the detailed discussion immediately after a representative had promoted Zoton FasTab meant that the service was linked to the promotion of Zoton FasTab. This would be the impression given to GPs. The role of the representative was thus unacceptable and a breach of the Code had been ruled.

Turning to the present case, Case AUTH/1655/11/04, the Panel noted that its ruling in Case AUTH/1652/11/04 was the subject of an appeal by Wyeth to the Code of Practice Appeal Board. At the date of consideration of the present case the appeal in Case AUTH/1652/11/04 had not been heard.

The Panel noted Wyeth's submission that the representative did not conduct the discussion in accordance with the company's approved procedure for the introduction of the GastroCare Service; the representative should have started from the beginning when introducing the service to the complainant. The Panel also noted that the effect of its ruling in Case AUTH/1652/11/04 was such that even if company procedures had been followed the representative's conduct would still have been unacceptable in relation to the requirements of the Code. Both the representative at issue and the overall arrangements linked the provision of the service to the promotion of Zoton FasTab; this was unacceptable in relation to the requirements of the Code. A breach of the Code was ruled.

A practice pharmacist complained about the conduct of a representative from Wyeth Laboratories.

As the case involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority to ensure compliance with undertakings. This accorded with advice previously given by the Code of Practice Appeal Board.

COMPLAINT

The complainant stated that during October 2004 a Wyeth representative visited the complainant's practice and spoke to a general practitioner about Zoton FasTab (lansoprazole). The GP asked the representative to return later and speak to the practice manager. When the representative returned the practice manager asked the complainant to be present for the meeting.

The representative explained that Zoton FasTab was cheaper than the equivalent capsules and that the practice could save money by switching. She quoted a typical figure of £6000 per year. The complainant explained that the practice was more interested in reviewing the dose of proton pump inhibitors (PPIs) rather than the choice of medicine. She replied that she could engage the services of a third party, for which there would be no charge to the practice, to facilitate a change from capsules to FasTab. She left two leaflets entitled 'Zoton FasTab – We've come to expect more for less …' and 'Zoton FasTab – Potential cost savings per year (£) – Zoton FasTab vs lansoprazole capsules' and a GastroCare – GP Systems Specialist Implementation (GPSSI) pack.

The practice manager stated that they would discuss the proposal and have an answer the following week. After discussion with the doctors, it was decided not to proceed.

The complainant was concerned that Wyeth continued to offer support to practices for switching to a specific product. It appeared that Wyeth had not changed its promotional activities following the ruling against it during the summer [Case AUTH 1561/3/04].

When writing to Wyeth, the Authority asked it to respond in relation to Clauses 2, 9.1, 18.1 and 22.

RESPONSE

Wyeth stated that it had fully complied with the undertaking given in the previous case, Case AUTH/1561/3/04. The Formulary Based Implementation (FBI) Service and all associated materials in respect of which the undertaking was given were withdrawn with immediate effect from the sales force by a memorandum and the service had not been offered or materials used since June 2004. Wyeth referred to a memorandum (reference WZZOT/2004/0018) and associated forms of undertaking, all of which were completed in accordance with the procedure stated therein. The service offering to which the present complaint related was part of the new service offering, as described below, which Wyeth subsequently designed and developed in order to avoid any further breaches of the Code following the outcome of Case AUTH/1561/3/04. Wyeth considered that this service offering and associated material complied with the Code.

Wyeth's service range in the gastrointestinal therapy area had been redesigned and developed, and the new range launched, so that all such services were non-brand specific and therefore could be offered and performed in respect of any relevant brand of medicine (ie proprietary or generic) of the GP's choice. Further, the new material and the material use sequence now made it clear that the GP's prescribing decision had been made in advance of any offer of a service to assist in implementing that decision being made by Wyeth. The Wyeth service offering now clearly fell under the provisions of Clause 18.1 of the Code and its supplementary information which allowed the provision of medical and educational services to enhance patient care or benefit the NHS as long as they were not provided in such a way as to be an inducement to prescribe any medicine.

The company's designated procedure was as follows:

The GP expressed an interest in a review of their or their practice's PPI prescribing.

In a visit separate to any product-related visit, or in a clearly separated part of the same visit, and following confirmation from the GP that they had an interest in a review of their or their practice's PPI prescribing, the representative followed the procedure as set out in the representative briefing document 'Action Plan: GastroCare Service Offerings' (ZZOT3580), the relevant pages of which were provided. Briefly, the GP completed and signed the medication review spreadsheet to illustrate the prescribing decision s/he had made or was making and wanted to implement. If the GP only wanted to change from one formulation of the same PPI to another in a dose for dose switch, then the representative offered the GPSSI service, using the GPSSI pack (ZZOT3588) as attached by the complainant in this case, to show the GP how the service would be carried out. If the GP accepted the service offering, (s)he completed the practice booking and consent form and the Wyeth representative then arranged an external supplier to carry out the service at the practice.

In this case, the representative twice discussed Zoton FasTab with the GP. In a third, separate meeting the GPSSI service was discussed, at the end of which the GP expressed an interest in the GPSSI service, but asked the representative to discuss it further with the practice pharmacist. The representative then discussed the GPSSI service in a further, separate meeting with both the practice manager and practice pharmacist, and on specific request from the practice the GPSSI pack (ZZOT3588) was left so that it could be discussed further in a meeting with other GPs in the practice.

Based on the above, Wyeth considered that it had complied with the undertaking given in Case AUTH/1561/3/04 and accordingly had maintained high standards and had not brought discredit upon or reduced confidence in the pharmaceutical industry.

In response to a request for further information Wyeth explained that the representative at issue did not conduct the discussion about the GPSSI Service with the practice manager and the practice pharmacist (the complainant) in accordance with the company's approved procedure for the introduction of the GastroCare Service. Whilst the representative was asked by the GP to talk to the practice manager about the GPSSI service, when the practice pharmacist joined the meeting the representative should have started from the beginning in introducing the

GastroCare service. She should then have only continued with discussion on specific elements of the service following clarity that this was what was required by the practice personnel. It was apparent that the complainant did not have a clear PPI prescribing decision in mind and that the discussion moved onto the relative benefits of Zoton FasTab. The service discussion should not have continued in these circumstances.

In failing to comply with Wyeth's approved procedure for the introduction and offer of the GastroCare service, the representative had missed out key elements of the GastroCare service discussion intended to ensure that the offer of the service did not, and there could be no perception that it might, unacceptably induce a prescribing decision or recommendation. In the circumstances of the combination of factors present in this case Wyeth acknowledged that the representative had not offered the service in accordance with the requirements of Clause 18.1. Further guidance and training would take place to address the learnings from this complaint.

Wyeth considered that in substantially reviewing its service offering, in developing new and bespoke training materials for this and in delivering that training to all involved in the discussion and delivery of this new service, it had complied with the undertaking given in respect of Case AUTH/1561/3/04, and accordingly had maintained high standards and had not brought discredit upon or reduced confidence in the pharmaceutical industry.

PANEL RULING

The Panel noted that the complainant had, *inter alia*, alleged a breach of the undertaking given by Wyeth in Case AUTH/1561/3/04 which concerned a switch programme whereby patients on Zoton capsules were switched to Zoton FasTab; breaches of Clauses 9.1 and 18.1 of the Code were ruled.

The Panel considered that its ruling in a previous case, referred to by Wyeth, Case AUTH/1606/7/04 which considered whether arrangements for Wyeth's revised switch programme were in breach of the undertaking given in Case AUTH/1561/3/04 was relevant here.

Panel Ruling in Case AUTH/1606/7/04

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 the industry that companies complied with undertakings.

The Panel noted that the previous case, Case AUTH/1561/3/04, concerned the Formulary Based Implementation (FBI) service whereby patients on Zoton capsules were switched to Zoton FasTab. The Panel had considered that the FBI Service was part of the promotion of Zoton FasTab; it was not described as anything else in the material. The service could thus not benefit from the supplementary information to Clause 18.1 regarding the provision of medical and educational goods and services. The Panel noted Wyeth's submission that Zoton FasTab was 10% less expensive than Zoton capsules. Switching patients from Zoton capsules to Zoton FasTab was thus a less expensive way of prescribing Zoton. Companies could of course promote products on the basis of cost and it was not unreasonable to note savings that a practice might make by switching from one product to another. The difficulty was when the company paid directly or indirectly for those changes to be made because then the company's actions amounted to it paying to boost the prescription of a specific medicine. In this regard, the Panel noted that the switch programme at issue involved two products marketed by the same company; prescriptions for Zoton FasTab were not being generated at the expense of another company's product. Nonetheless, Clause 18.1 of the Code stated that 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend or buy any medicine, subject to the provisions of Clause 18.2'. Thus in the Panel's view it was immaterial that the two medicines at issue were marketed by the same company. The provision of the FBI Service by Wyeth would benefit a practice by saving it the expense of carrying out the switch itself. The arrangements amounted to a pecuniary advantage given as an inducement to prescribe Zoton FasTab. Breaches of Clauses 9.1 and 18.1 had been ruled.

The Panel noted that there were differences between the switch programme at issue in Case AUTH/1561/3/04 and the service at issue in the present case, Case AUTH/1606/7/04; the present service was not restricted to a switch from Zoton capsules to Zoton FasTab but was available for any oral PPI of the doctor's choice. The Panel noted Wyeth's submission that the prescribing decision of the GP had to be made in writing in advance of the offer of the service. The medication review booklet (ref ZZOT3587) explained that the Gastrocare service was available to review any oral PPI dose at the request of the practice. The representatives' 'Action plan: Gastrocare service offerings' explained that if the GP chose to change from one formulation of a PPI medication to another in a dose for dose switch, the most suitable service was the GP System Specialist Implementation. If any other change was required, or if the GP did not wish for this service, the GP was offered the Gastrocare audit review.

The Panel noted that representatives were instructed that all practices signed up under the withdrawn FBI service must be re-signed under the new service. The regional business managers had been told why the previous service was withdrawn and instructed the representatives in relation to the revised service. Representatives had to confirm that documentation in relation to the original service was returned to head office or destroyed locally.

The Panel noted Wyeth's submission that the complainant had requested a review of his PPI prescribing from Zoton to Zoton FasTab and had informed the representative at the outset that this prescribing decision had been agreed with the

relevant PCT. The Panel also noted Wyeth's submission that the medication review spreadsheet was completed and signed before any service offerings were discussed.

The booklet GP Systems Specialist Implementation Pack (ref ZZOT3585) explained the role of the GP Systems Specialist in relation to the implementation of the GP prescribing requests as set out in the medication review spreadsheet. Wyeth submitted that this was the procedure to be implemented in the complainant's practice. No details were provided about the alternative service, the Gastrocare audit review. The Panel noted, however, that it was not the subject of complaint.

The Panel considered the arrangements only in relation to the alleged breach of undertaking. It did not consider the arrangements in relation to the requirements of Clause 18.1; it had no complaint in that regard. The Panel considered that the service at issue was sufficiently different from that considered in Case AUTH/1561/3/04; the service was no longer restricted to switches from Zoton capsules to Zoton FasTab but was available for all oral PPIs. The Panel considered there was no breach of the undertaking previously given. The Panel had therefore ruled no breach of Clause 22. It thus followed there had been no breach of Clauses 9.1 or 2.

Case AUTH/1655/11/04

In relation to the alleged breach of undertaking the Panel noted Wyeth's submission that the material and service offering at issue in the present case were the same as those considered in Case AUTH/1606/7/04. The Panel thus considered that its ruling in Case AUTH/1606/7/04 applied here. No breach of Clauses 22, 9.1 and 2 was thus ruled.

In relation to the allegations about the conduct of the representative the Panel noted that a previous case, Case AUTH/1652/11/04 considered the role of the representative and the revised service.

Panel Ruling in Case AUTH/1652/11/04

The Panel noted the various matters identified and taken up as a complaint with Wyeth under Paragraph 17 of the Constitution and Procedure. The Panel noted that Wyeth had agreed to withdraw the Gastrocare Process Flow Chart. The Panel noted that, as previously explained to Wyeth, the matter taken up under Paragraph 17 related to the Panel's concerns about the cumulative effect of the arrangements regarding the role of the representative and the impression given to GPs and this remained before it for consideration.

The Panel noted that Wyeth maintained that its representatives could introduce the service in a clearly distinct and separate part of the same GP call as the promotion of Zoton FasTab provided no product promotion took place during the Gastrocare service discussion.

The Panel noted the process to be followed by the Wyeth representatives when calling on GPs. The representative had two functions, firstly to promote Zoton FasTab and secondly to offer the Gastrocare Service. The product promotion part of the call was closed by means of the approved closing statement 'Is there any reason why you wouldn't start saving NOW and change all those patients on lansoprazole capsules to Zoton FasTab?'. Representatives were then to move on to the next part of the call. As part of the introduction to the service the GP was asked if they wanted to implement a PPI medication review. If so the GP was asked to identify the changes they wished to be implemented and to complete the Medication Review Spreadsheet. The Panel noted Wyeth's submission that previously it had stated that the prescribing decision was made in writing in advance of the service offering and this was done by completion of the Medication Review Spreadsheet. Wyeth now stated that this was not so and the spreadsheet completion was part of the service offering part of the call. The Panel was extremely concerned that Wyeth had changed its submission. Further it was not clear whether Wyeth's latest submission meant that the prescribing decision was not made in writing in advance of the service offering or that the prescribing decision was not made in writing by means of completion of the Medication Review Spreadsheet.

The Gastrocare Process Flowchart instructed representatives to sell Zoton FasTab and close.

The flowchart used the example '… is there any reason why you wouldn't change your existing lansoprazole capsule patients to Zoton'. The next part of the flowchart stated 'Wyeth offers a single GastroCare service to help you achieve such medication review objectives'. The flowchart used the example 'This Medication Review table shows the various PPI options. If you indicate which ones you want to implement, I can then talk about the appropriate method to do that, since the method of implementation differs depending on the PPI prescribing decision'. The flowchart then stated 'Doctor(s) completes and signs the Medication Review'. This was accompanied by the instruction that representatives were not allowed to influence the doctor during the discussion on medication review. The flowchart then instructed the representatives to offer the most appropriate part of the service relevant to the completed medication review. Reference was made to the Gastrocare Service Decision Tree.

The Gastrocare Service Decision Tree instructed representatives that 'Once Zoton FasTab has been fully and effectively sold and switch closed…' followed by a box containing 'Wyeth offers a single Gastrocare service to help you achieve such medication review objectives. This Medication Review table shows the various PPI options. If you indicate which ones you want to implement, I can then talk about the appropriate method to do that since the method of implementation differs depending on the PPI prescribing decision'. Three possible options were outlined. Firstly PPI change of formulation only, secondly any PPI medicine change and thirdly any PPI dose change.

The Panel noted the supplementary information to Clause 18.1 of the Code that the provision of medical and educational goods and services which would enhance patient care and benefit the NHS was not

prevented by Clause 18.1. The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine. The Panel also noted the advice that if representatives provided, delivered or demonstrated medical and educational goods and services then this must not be linked in any way to the promotion of medicines.

The Panel did not consider that the arrangements for the promotion of Zoton FasTab and the offer of the service by the representative were sufficiently separate. The discussion about Zoton FasTab concluded with a discussion about switching patients to it. The Panel considered that the subsequent introduction of a switch service by the representative would not be seen as sufficiently separate to the promotional discussions about switching to Zoton FasTab that immediately preceded it. The introduction of the service and the detailed discussion immediately after a representative had promoted Zoton FasTab meant that the service was linked to the promotion of Zoton FasTab. This would be the impression given to GPs. The role of the representative was thus unacceptable in relation to the requirements of Clause 18.1; a breach of Clause 18.1 had been ruled.

Case AUTH/1655/11/04

The Panel noted that its ruling in Case AUTH/1652/11/04 was the subject of an appeal by Wyeth to the Code of Practice Appeal Board. At the date of consideration of the present case the appeal in Case AUTH/1652/11/04 had not been heard.

The Panel noted Wyeth's submission that the representative did not conduct the discussion in accordance with the company's approved procedure for the introduction of the GastroCare Service; the representative should have started from the beginning when introducing the service to the complainant. The Panel also noted that the effect of its ruling in Case AUTH/1652/11/04 was such that even if company procedures had been followed the representative's conduct would still have been unacceptable in relation to the requirements of Clause 18.1. Both the representative at issue and the overall arrangements linked the provision of the service to the promotion of Zoton FasTab; this was unacceptable in relation to the requirements of Clause 18.1. A breach of Clause 18.1 was ruled.

Complaint received **16 November 2004**

Case completed **3 March 2005**

CASE AUTH/1656/11/04 *NO BREACH OF THE CODE*

PHARMACEUTICAL ADVISOR v AMDIPHARM

Computer memory stick as promotional aid

A pharmaceutical advisor at a primary care trust noted that the Code required gifts to be relevant to the practice of the recipient's profession. In this regard he queried the provision of computer memory sticks to general practitioners.

The Panel noted that the key feature of memory sticks was the ease with which data could be stored on them and thereby transferred from one computer to another. The Panel also noted Amdipharm's explanation that the memory stick could be used to access clinical or medicines-related data and for the carriage of lecture or presentation material.

On balance the Panel considered that a memory stick was sufficiently relevant to the practice of medicine. No breach of the Code was ruled.

A pharmaceutical advisor at a primary care trust (PCT) had previously complained about the provision of a 65MB memory stick as a promotional aid for Detrunorm (propiverine) by Amdipharm plc, Case AUTH/1640/10/04, wherein the Panel had ruled no breach of Clause 18.1 with regard to the cost of the memory stick. On receipt of the Panel's ruling the complainant raised an additional concern which was taken up as the present complaint; Case AUTH/1656/11/04.

COMPLAINT

The complainant noted that in Case AUTH/1640/10/04 the Panel did not consider that it had been required to determine whether memory sticks were relevant to the practice of medicine. The complainant stated that he had intended to draw attention to both explicit requirements of Clause 18.2 ie that gifts or prizes should be inexpensive and relevant to the practice of the recipient's profession. He queried the relevance of memory sticks to the practice of medicine.

Amdipharm was thus asked to respond in relation to the requirements of Clause 18.1 of the Code.

RESPONSE

Amdipharm explained that the memory sticks were sent to general practitioners who had completed and returned a reply paid card.

Amdipharm considered the memory stick to be of particular relevance to the practice of medicine as it provided a lightweight method of accessing 64MB of data. These could be clinical data or medicines-related data eg word documents including a summary of product characteristics, patient information leaflets or patient orientated literature. One particular use for a memory stick was in education and training and the carriage of lecture or presentation material including powerpoint slides relating to clinical, scientific or general topics. The memory stick was of value to transfer such material from one computer to another for presentations, and as such was the equivalent of a floppy disk (1.44MB) but with more capacity (64MB) for powerpoint slides.

Amdipharm noted that the Medicines Control Agency [now the Medicines and Healthcare products Regulatory Agency] guidance to the advertising regulations, the Advertising and Promotion of Medicines in the UK, stated that the criterion of 'relevance' was met by items which had a general business use such as, *inter alia*, inexpensive computer accessories. Amdipharm suggested that the term 'inexpensive computer accessories' included such items as a memory stick, mouse, mouse-pad or wrist-cushion.

The company trusted that it had provided sufficient background and rationale for its use of the memory stick in the way prescribed, and that it satisfied both requirements of being inexpensive and relevant to the practice of medicine.

PANEL RULING

The Panel noted that Clause 18.1 required promotional aids to be *inter alia* relevant to the practice or employment of the recipient's profession. The Panel noted that the memory sticks had been provided to general practitioners. The Panel noted that the key feature of memory sticks was the ease with which data could be stored on them and thereby transferred from one computer to another; particularly for presentations. The Panel also noted Amdipharm's explanation that the memory stick could be used to access clinical or medicines-related data and for the carriage of lecture or presentation material.

On balance, the Panel considered that the provision of a memory stick was sufficiently relevant to the practice of a GP's profession or employment. No breach of Clause 18.1 was ruled.

Complaint received **22 November 2004**

Case completed **20 January 2005**

CASE AUTH/1657/11/04 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER/PHARMACEUTICAL COMPANY CONSULTANT v ASTRAZENECA

Invitation to a meeting

A consultant to several pharmaceutical companies, including Bristol-Myers Squibb, complained in her capacity as a general practitioner about a meeting invitation which she had received through the post from AstraZeneca. The complainant noted that the envelope bore no indication that the item was from a pharmaceutical company; indeed the wording 'ADDRESSEE ONLY' stamped in red on the front implied that there was something important and serious inside. The complainant also considered that the title of the meeting 'Lies, Damn Lies & Statins' was derogatory to the medical profession.

The Panel noted that the invitation to attend the meeting on statins had been sent in an envelope which was blank apart from the words 'ADDRESSEE ONLY' above the address window. The Panel considered that such wording drew attention to the envelope but did not imply that its contents were important or serious. The text on the envelope was such that recipients would have no expectation as to its content. The enclosed invitation was not, in itself, promotional material for AstraZeneca's statin. The Panel did not consider that the envelope constituted disguised promotion as alleged. No breach of the Code was ruled.

With respect to the title of the meeting the Panel did not consider that the majority of recipients would find it derogatory or that in choosing it AstraZeneca had failed to maintain high standards. No breach of the Code was ruled.

A consultant to several pharmaceutical companies, including Bristol-Myers Squibb, complained in her capacity as a general practitioner, about a meeting invitation which she had received through the post from AstraZeneca UK Limited (ref 14689D). The invitation had been sent to general practitioners and a small number of practice nurses and prescribing advisors between September and mid November 2004.

COMPLAINT

The complainant noted that on the envelope in which the invitation was sent there was no indication that the item was from a pharmaceutical company; indeed the wording 'ADDRESSEE ONLY' stamped in red on the front implied that there was something important and serious inside.

The complainant also considered that the title of the meeting 'Lies, Damn Lies & Statins' was derogatory to the medical profession.

When writing to AstraZeneca the Authority asked it to respond in relation to Clauses 8.2, 9.1 and 10.1 of the Code.

RESPONSE

AstraZeneca stated that as the invitations were intended solely for medical professionals the envelopes bore the words 'ADDRESSEE ONLY' to prevent them being opened by, for example, receptionists who were not medical professionals and for whom the contents were not appropriate under the Code.

The words 'ADDRESSEE ONLY' did not imply that the contents were particularly important or serious. They implied, as intended, that the contents were relevant and appropriate only for the addressee. AstraZeneca therefore did not consider that the material was disguised promotion in breach of Clause 10.1.

The overall appearance of the envelope and contents was not out of keeping with material sent regularly to medical professionals by the industry and which was judged to be suitable for them. Therefore, AstraZeneca did not consider that the material was in breach of Clause 9.1.

With regard to the allegation that there was no indication on the envelope that the item was from a pharmaceutical company, AstraZeneca noted that the invitation itself contained a clear declaration of sponsorship on the front, inside and back page. The company did not consider that it was a requirement, nor was it common practice, to declare sponsorship on an envelope containing an invitation. Therefore the material did not constitute disguised promotion and was not in breach of Clause 10.1.

AstraZeneca submitted that the title of the meeting 'Lies, Damn Lies & Statins' was a playful reference to the well known saying 'lies, damn lies and statistics'. As such it referred to the widespread attention and media interest in this area that had led to misunderstandings and misperceptions of statins. There was nothing in the title that could be construed as specifying or implying criticism of medical professionals. AstraZeneca provided a copy of the presentation which it stated bore this out. From this, AstraZeneca considered that it would be apparent that this material was not derogatory to the medical profession and was not in breach of Clauses 8.2 or 9.1.

PANEL RULING

The Panel noted that the invitation to attend the meeting on statins had been sent in an envelope which was blank apart from a bold red stamp above the address window which read 'ADDRESSEE ONLY'. The Panel considered that such wording drew attention to the envelope but did not imply that there was something important and serious inside. The text on the envelope was such that recipients would have no expectation as to its contents. Although the enclosed invitation referred to a meeting

on statins sponsored by AstraZeneca, the invitation was not, in itself, promotional material for AstraZeneca's product Crestor (rosuvastatin). The Panel did not consider that the envelope constituted disguised promotion as alleged. No breach of Clause 10.1 was ruled.

The Panel did not consider that the majority of recipients would find the title of the meeting 'Lies, Damn Lies & Statins' derogatory or disparaging. No breach of Clause 8.2 was ruled. The Panel did not consider that, with respect to the title of the meeting, AstraZeneca had failed to maintain high standards. No breach of Clause 9.1 was ruled.

Complaint received **25 November 2004**

Case completed **27 January 2005**

CASE AUTH/1658/11/04

GENERAL PRACTITIONER v LUNDBECK

Arrangements for a meeting

A general practitioner alleged that the main purpose of a meeting, held at an exclusive local restaurant and sponsored by Lundbeck, was hospitality and that this was excessive for a half hour meeting.

The Panel noted that the complainant had not attended the meeting in question, the complaint had been made on the basis of the invitation sent by Lundbeck which stated that a case study discussion would be hosted by a local consultant psychiatrist. The stated programme was: 7pm, Welcome and Introduction; 7.30pm, Case study discussions; 8pm, Dinner. The impression thus given by the invitation was that a one hour meeting would be followed by dinner. There was no mention that the meeting was to be held in a private room to enable medical discussions to continue over dinner.

The Panel noted that although the formal part of the meeting as described on the agenda had lasted only one hour, Lundbeck had stated that the discussion had lasted most of the evening, with questions and answers concluding at around 10.45pm. The meeting had taken place in a private room and had cost approximately £34 per head. The Panel considered that the level of hospitality was acceptable under the Code and that, on balance, it was secondary to the purpose of the meeting. Nonetheless, the invitation gave the opposite impression and it was on this basis that the Panel ruled a breach of the Code. High standards had not been maintained and a further breach of the Code was ruled. The Panel did not consider that the invitation warranted particular censure and so no breach of Clause 2 was ruled.

COMPLAINT

A general practitioner stated that Lundbeck had invited him to attend a local meeting at one of the most exclusive restaurants in the area. The complainant alleged that the main purpose of the meeting was hospitality and this was excessive for a half hour meeting.

When writing to Lundbeck the Authority asked it to respond in relation to the requirements of Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

Lundbeck submitted that the meeting organised in a private function room at the restaurant was not in breach of the Code.

Forty-eight local psychiatrists and general practitioners were invited to the scientific meeting. The restaurant was chosen as the venue principally due to its central location for those invited, ease of access via local transport links and the availability of a private function room in which to host the educational meeting. Eight clinicians and two medical representatives attended the meeting.

The cost of the meeting, approximately £34 per head, included dinner, a glass of wine and the service charge. Lundbeck submitted that the cost per head was not excessive, and the level of hospitality was appropriate for the specialist psychiatrists and general practitioners who attended. Lundbeck provided relevant receipts.

Lundbeck submitted that the scientific content of the meeting, although in an informal setting was of the highest standard consisting of the following: one of the representatives introduced the main speaker, a local consultant psychiatrist, and started the discussion by briefly presenting two scientific papers from peer reviewed journals concerning the pharmacological treatment of major depressive disorder, comparing the use of escitalopram [Lundbeck's product Cipralex] and venlafaxine XL [Wyeth's product Efexor XL]. Copies of the papers and summaries of product characteristics (SPCs) were available. At 7.30 pm, the consultant psychiatrist presented specific case studies from her extensive experience. The delegates then produced their own cases for discussion. The actual meeting with a local expert generated so much interest that questions and answers continued throughout the meal, and long afterwards until approximately 10.45 pm. Lundbeck provided a statement from the consultant psychiatrist stating exactly what had occurred. Lundbeck stated that if the complaint had come from a delegate who had attended the meeting he/she would be able to corroborate the account of events.

Lundbeck submitted that its intention had always been that the educational content of the meeting would continue throughout the evening, to include a

discussion during the course of the meal, and this was indeed what transpired.

In conclusion, Lundbeck did not consider that the meeting was held at an inappropriate venue; the level of hospitality was appropriate and secondary to the educational content of the meeting.

In response to a request for further information Lundbeck stated that the entire meeting, including dinner, was held in a private function room. A copy of a letter from the restaurant's management confirming this was provided.

PANEL RULING

The Panel noted that the complainant had not attended the meeting in question, the complaint had been made on the basis of the invitation sent by Lundbeck. The invitation, headed 'Treatment of Depression', stated that a case study discussion would be hosted by a consultant psychiatrist at a local restaurant. The stated programme was: 7pm, Welcome and Introduction; 7.30pm, Case study discussions; 8pm, Dinner. The impression thus given by the invitation was that a one hour meeting would be followed by dinner. There was no mention that the meeting was to be held in a private room to enable medical discussions to continue over dinner.

The Panel noted that although the formal part of the meeting as described on the agenda had only lasted one hour, Lundbeck stated that the discussion had lasted most of the evening, with questions and answers concluding at around 10.45 pm. The meeting had taken place in a private room and had cost approximately £34 per head. In the Panel's view the level of hospitality had not exceeded that which the recipients would normally adopt when paying for themselves. On balance the Panel also considered that the hospitality provided was secondary to the purpose of the meeting. Nonetheless, the invitation gave the opposite impression and it was on this basis that the Panel ruled a breach of Clause 19.1 of the Code. The Panel also considered that in relation to the invitation high standards had not been maintained and ruled a breach of Clause 9.1. The Panel noted that Clause 2 of the Code stated that, *inter alia*, activities associated with promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry. A ruling of a breach of Clause 2 was a sign of particular censure and was reserved for such circumstances. The Panel did not consider that the invitation was such as to warrant a ruling of a breach of this clause.

Complaint received **26 November 2004**

Case completed **21 January 2005**

CASE AUTH/1660/12/04 *NO BREACH OF THE CODE*

AVENTIS PASTEUR MSD v GLAXOSMITHKLINE

Offer of compensation for cancelled orders

Aventis Pasteur MSD complained that after GlaxoSmithKline had had to cancel some orders for its influenza vaccine Fluarix, the company had written to one of the general practitioners affected to offer money in recognition of the additional administration and inconvenience caused. The letter ended by asking the recipient to consider placing their influenza vaccine orders with GlaxoSmithKline next year. Aventis Pasteur MSD stated that juxtaposing the offer of reimbursement and the request to consider placing a future order implied that the two were linked. Aventis Pasteur alleged that a pecuniary advantage had been offered as in inducement to purchase Fluarix in breach of the Code. The company further alleged that such action potentially brought discredit upon the pharmaceutical industry in breach of Clause 2.

The Panel noted that the letter had been sent to customers because a general shortage of influenza vaccine had led GlaxoSmithKline, at short notice, to cancel some orders for Fluarix. Affected practices would have had no alternative but to try and obtain influenza vaccine from another, more expensive, source. In the Panel's view the payment offered by GlaxoSmithKline was not unreasonable compared to the disruption caused and the costs incurred; it was clearly described as a goodwill gesture. The practice was to receive the money; GlaxoSmithKline submitted that general practitioners were not to be paid personally as alleged. The Panel did not consider that in this instance the payment of compensation was an inducement to prescribe, supply, administer, recommend or buy any medicine. The payment would improve GlaxoSmithKline's reputation with those customers which it had let down, such that they might consider ordering influenza vaccine from the company next year, but the letter did not imply that the payment of the compensation was dependent upon the receipt of future orders. The Panel did not consider that the compensation, or the way it had been offered, constituted a payment that was unacceptable under the Code. The Panel ruled no breach of the Code.

Aventis Pasteur MSD Ltd complained about a letter (ref FLX/LTR/04/15711/1) sent by GlaxoSmithKline UK Ltd to a general practitioner. The letter referred to GlaxoSmithKline's cancellation of the recipient's order for influenza vaccine (Fluarix) and offered a payment of £440 to recognise the additional administration and inconvenience caused. The letter went on to solicit an order for influenza vaccine for the following year stating that the practice's account would be flagged as high priority.

COMPLAINT

Aventis Pasteur MSD explained that influenza was a winter illness and vaccination was recommended for all those aged 65 years and over, as well as for those with certain chronic medical conditions. Due to the capacity of the influenza virus to change its antigenic makeup, the vaccine was usually different each year – hence the need for annual vaccination. In the UK vaccination usually took place between September and November. Six companies normally supplied influenza vaccine to the UK market. In 2004, just before vaccine was due to be distributed to customers, one of the manufacturers (Chiron) had its manufacturing licence temporarily suspended by the Medicines and Healthcare products Regulatory Agency. As a result Chiron, which historically supplied about 20% of the UK market, was unable to supply any doses for the 2004 season. At a very late stage, therefore, there was a significant shortfall in supply not just in the UK but also elsewhere. With varying degrees of success, the remaining companies tried to absorb the additional demand.

GlaxoSmithKline, due to what it cited as 'unprecedented demand' for Fluarix, cancelled a number of orders placed by UK customers. The letter at issue was sent by GlaxoSmithKline's National Sales Manager for vaccines to a customer who had ordered influenza vaccine from Chiron but then ordered from GlaxoSmithKline following Chiron's withdrawal from the market. This was one of the orders GlaxoSmithKline then cancelled.

The letter was sent to the general practitioner unsolicited. It offered the addressee an apparently (at least to the recipient) arbitrary sum of £440 'to recognise the additional administration and inconvenience caused by cancellation of your order'. Furthermore, it stated that the payment would be sent by cheque, presumably payable to the GP personally. Finally, after offering £440 the recipient was asked to consider placing their influenza vaccine order with GlaxoSmithKline for next year. Aventis Pasteur MSD's medical director spoke to the practice manager at the practice concerned. She was very concerned at the nature of the letter and described it as 'bribery'.

Aventis Pasteur MSD raised the matter with GlaxoSmithKline and a copy of the correspondence between the companies was provided. In brief, all customers whose orders were cancelled were offered reimbursement according to a formula described by GlaxoSmithKline as 'a low fixed amount plus a nominal sum per dose ordered'. Further information was not provided but this customer's order was for 850 doses.

Aventis Pasteur MSD stated that, as submitted by GlaxoSmithKline, it was true that the payment offered was not overtly conditional upon placing a future order for Fluarix. However, juxtaposing the offer of reimbursement and the request to consider placing a future order with GlaxoSmithKline implied that the two were linked. This was certainly the impression left with the practice manager concerned. Aventis Pasteur MSD therefore alleged that a pecuniary advantage had been offered that could be seen as an inducement to purchase Fluarix in the future in breach of Clause 18.1.

Aventis Pasteur MSD noted that an unsolicited offer of a significant sum of money to a health professional

in the form of a cheque was included in the same letter as an attempt to secure a future order. GlaxoSmithKline sought to justify the unsolicited approach by arguing that it wished to treat all those affected in the same way. However, it was unlikely that every customer would have been affected in the same way. Those that had 'complained vociferously' were likely to be those who had been significantly inconvenienced (and might also have incurred significant costs). On the other hand, those that had made no complaint were unlikely to have suffered significant disruption (or incurred significant costs). To offer a significant cash sum to the latter and seek their order for 2005 had, in this case, been perceived by the customer as an inducement to purchase. Aventis Pasteur MSD alleged that this had the potential to bring discredit upon the pharmaceutical industry in breach of Clause 2.

RESPONSE

GlaxoSmithKline stated that following the withdrawal of Chiron's licence to supply influenza vaccine on 5 October 2004, GlaxoSmithKline experienced unprecedented demand for Fluarix in the UK and around the world. Unfortunately, the company was unable to fulfill all of the orders placed during this period because of the rapidity of orders arriving through multiple channels, the overall shortage of influenza vaccine and the lead times involved in production. Despite this demand, GlaxoSmithKline was able to supply thousands of additional doses of Fluarix to the market to cover the shortage of overall stock. Those UK practices whose orders GlaxoSmithKline was unable to fill were notified of the cancellations on 27 October 2004.

The customer letter in question was sent on 11 November 2004 to the 67 practices whose Fluarix orders GlaxoSmithKline had had to cancel. In cases such as this the GP practice was GlaxoSmithKline's customer, purchasing vaccine, and the prescriber. The Fluarix customer letter was part of an ongoing communication between GlaxoSmithKline and these customers during this difficult time.

Practices arranged special influenza clinics to ensure efficient use of practice nurse time and advertised these to their patients using mailings and telephone campaigns. Consequently, reliability of supply was a key factor in choosing which brand of influenza vaccine to buy. Unlike most other branded pharmaceuticals, influenza vaccine promotion was based on service and delivery, as well as price, rather than safety or efficacy. Following the cancellation of the Chiron licence and GlaxoSmithKline's inability to fulfill customer orders, the affected practices would have had to spend time and incur cost in re-arranging the influenza clinics (for example the cost of making telephone calls or postage costs of sending letters to each affected patient and stationery expenses).

Time and costs would also have been incurred by the affected practices to obtain replacement vaccine. Fluarix was the lowest priced influenza vaccine apart from one manufactured by Chiron. Any replacement vaccines bought by a practice after GlaxoSmithKline had cancelled the order would necessarily be from a higher-priced manufacturer. GlaxoSmithKline provided a list of the available vaccines together with their prices.

Despite fulfilling many additional last minute requests for influenza vaccine GlaxoSmithKline was unable to fulfill some Fluarix orders which thus had to be cancelled. Subsequently the company had received several complaints, some threatening legal action, regarding the associated inconvenience and additional costs incurred as a result of the cancellation.

GlaxoSmithKline decided to reimburse all affected customers for these additional costs. All practices would have incurred these additional costs, and the bigger the cancelled order, the greater the cost to the practice. GlaxoSmithKline thus decided on a simple formula of £100 plus £0.40/dose ordered to all affected practices in an equitable manner. As GlaxoSmithKline did not consider that it was liable contractually to compensate the affected customers for these costs the reimbursement was described as a 'goodwill gesture'.

The 'significant cash sum' referred to by Aventis Pasteur MSD (£440) reflected the size of the order from the practice in question (ie £100 fixed fee + 850 doses at £0.40). When compared to the cost of a first class stamp, the reimbursement of 40 pence per dose, which would also cover stationery expenses and administrative time, was not excessive.

GlaxoSmithKline considered that it was reasonable to offer this reimbursement to all practices whose orders had been cancelled and that it was fair to deal with all affected customers equally, rather than just those who complained. Reimbursement was based on the size of the order cancelled as this provided a more objective measure of the disruption and costs incurred. The reimbursement was offered in a cheque to the practice (not the individual) and was not conditional on future orders. The final paragraph made it explicitly clear that GlaxoSmithKline was not expecting the practice to feel inclined to order vaccine from it for next season, but the company took the opportunity to let the practice know that the company would work harder for it next year. The final paragraph of the letter read:

> 'I appreciate you may not feel able to do this, but if you would like place your order for flu vaccine with GlaxoSmithKline for 2005 we offer a number of packages, with excellent service and profitability for your Practice. We are keen to ensure all runs smoothly for your flu clinics next year and therefore your account is flagged as high priority. Further information can be obtained from your local representative or the Customer Contact Centre on [telephone number].'

There was no pecuniary advantage or financial inducement, but there was the promise of excellent service to a customer. GlaxoSmithKline denied a breach of Clause 18.1 as no financial advantage was offered.

GlaxoSmithKline stated that it was not aware of any other practices which had interpreted the Fluarix customer letter in the same way as the one Aventis Pasteur MSD has been in touch with. The letter offered the practice, not the individual, £100 plus

£0.40/dose cancelled in recognition of the additional administration time and costs that would be incurred as a result of the cancellation. There were no strings attached to the offer. It was not conditional on future orders and was described as 'a goodwill gesture'. A goodwill gesture was one which was given without expectation of anything in return.

The letter was not 'unsolicited' as described by Aventis Pasteur MSD; it was part of the ongoing communication between GlaxoSmithKline and its customers purchasing vaccines.

In contrast to Aventis Pasteur MSD's assertion, GlaxoSmithKline did not consider it was necessarily those who complained more who would have been more affected by the cancellation. There could be a multitude of reasons why a practice decided not to complain despite significant inconvenience and cost. It might think it a waste of time and effort and might prefer to concentrate on the day-to-day tasks of running a busy practice, or it might not have got round to it yet. Some might complain more readily than others.

GlaxoSmithKline reasonably estimated that all practices affected would incur certain costs as a result of the cancellation. By taking a swift, simple and even handed approach, GlaxoSmithKline acted with integrity to put right something that had been out of its control due to the unprecedented demand, but that reflected poorly on the company. GlaxoSmithKline maintained high standards throughout in its dealings with all of its customers.

GlaxoSmithKline had used the final paragraph of the Fluarix customer letter to reiterate the high level of service these customers could expect if they decided to buy Fluarix next year. This was not a financial inducement. The company submitted that its actions were fair and responsible and strongly disagreed that it had brought the industry into disrepute. As such, GlaxoSmithKline did not consider it had breached Clause 2.

PANEL RULING

The Panel noted that the letter had been sent to customers in response to an unusual situation. Due to a general shortage of influenza vaccine, GlaxoSmithKline had had to cancel some orders for Fluarix which it had initially accepted. Affected practices would have had no alternative but to try and obtain influenza vaccine from another, more expensive, source. Practices were told of the situation in October which, according to Aventis Pasteur MSD, was in the middle of the 'vaccination season'. By way of compensation GlaxoSmithKline had decided to pay each affected practice £100 plus £0.40/dose cancelled. The Panel noted that the payment was described in the letter as a goodwill gesture. It thus appeared that GlaxoSmithKline had made the offer without expecting anything in return. It was also clearly stated that payment would be to the practice; GlaxoSmithKline submitted that GPs were not to be paid personally as alleged. Following the statement in the letter regarding payment, the final paragraph referred to the possibility of the reader ordering next year's supply of influenza vaccine from GlaxoSmithKline; it was implied that the company would ensure that the practice was not let down again.

In the Panel's view the payment was not unreasonable compared to the disruption caused and the costs incurred; it was clearly described as a goodwill gesture. The practice was to receive the money. The Panel did not consider that in this instance the payment of compensation was an inducement to prescribe, supply, administer, recommend or buy any medicine. The payment would improve GlaxoSmithKline's reputation with those customers which it had let down, such that they might consider ordering influenza vaccine from the company next year, but the letter did not imply that the payment of the compensation was dependent upon the receipt of future orders. The Panel did not consider that the compensation, or the way it had been offered, constituted a payment that was unacceptable under the Code. The Panel ruled no breach of Clauses 18.1 and 2 of the Code.

Complaint received **1 December 2004**

Case completed **7 February 2005**

CASE AUTH/1661/12/04

GENERAL PRACTITIONER v PFIZER

Conduct of representatives

A general practitioner complained that two representatives from Pfizer who had made appointments to see him on the same day each cancelled their appointment at very short notice.

The Panel noted that the supplementary information to the Code stated that 'Representatives must always endeavour to treat doctors' time with respect and give them no cause to believe that their time might have been wasted. If for any unavoidable reasons, an appointment cannot be kept, the longest possible notice must be given'. The Panel noted that the two representatives had cancelled appointments with the complainant at short notice. One appointment was cancelled at only two or three hours' notice. The other representative had cancelled her appointment the day before she was due to visit. Both representatives had been called away by their manager to attend the same meeting. The Panel had no information about this meeting or when the representatives were informed about it.

The Panel noted Pfizer's submission that meetings held at short notice on an *ad hoc* basis were, for the two representatives concerned, relatively frequent occurrences. This was unacceptable. Companies should ensure that they gave their representatives as much notice as possible of forthcoming meetings so that appointments did not need to be cancelled at short notice.

The Panel considered that the period of notice given by the representatives was too short. The event causing the cancellations of the appointments was within the company's control although not within the representatives' control. In the circumstances the Panel considered that high standards had not been maintained by the company. A breach of the Code was ruled. No breach of the Code was ruled with respect to the representatives' behaviour.

A general practitioner complained about the conduct of representatives from Pfizer Limited.

COMPLAINT

The complainant stated that in mid to late November a representative made an appointment to see him at 2pm on 7 December. On 6 December another Pfizer representative telephoned to make an appointment and the complainant agreed to see her also on 7 December at 10am.

The first representative then telephoned the complainant to cancel as she had an important meeting. On the morning of 7 December the second representative telephoned the complainant to cancel saying she had a meeting to go to.

The complainant wanted confirmation that Pfizer would not allow its representatives to act in such a disorganised manner.

When writing to Pfizer the Authority asked it to respond in relation to Clauses 9.1 and 15.4 of the Code.

RESPONSE

Pfizer stated that the complainant had muddled up the two representatives. The first one had not made her appointment about two weeks before but on the day before for 10am on 7 December. She cancelled early on the morning she was due to visit the complainant. The second representative had made her appointment for 2pm on 7 December about two weeks beforehand, not the day before, and cancelled her appointment the day before.

Both representatives cancelled their appointments and said that the complainant was polite and apparently satisfied with the situation, expressing no sign of anger. Both representatives had been called at short notice to a meeting by their manager. At the time they were on field-based training as they had only recently joined Pfizer. Meetings held at short notice on an *ad hoc* basis were, in their circumstances, relatively frequent occurrences. It was unfortunate that both representatives had independently arranged to see the complainant on the same day and were both called away to the same meeting.

Apparently another Pfizer representative, more experienced and already established in the territory, subsequently made an appointment and saw the complainant at 2pm on 7 December. Pfizer knew therefore that at least the complainant's later appointment was not wasted.

The first representative was new to the industry and was yet to take her ABPI examination. The second representative, although new to Pfizer, was an experienced representative and had passed her ABPI examination. The two representatives were working within different therapy areas and would not therefore necessarily be expected to coordinate their appointments completely.

Pfizer very much regretted the circumstances leading to the cancellation of two appointments on the same day but strongly believed that its representatives behaved quite correctly and professionally throughout. Pfizer refuted any suggestion of a breach of Clause 9.1.

With regard to Clause 15.4, these two representatives were new to the territory, to Pfizer and to its procedures, and worked in separate therapeutic areas. It, therefore, would not have been inappropriate for them both to make separate appointments to see a customer on the same day. Pfizer's experience of interpreting Clause 15.4 was largely around a single representative seeing a health professional too frequently. Pfizer did not see, therefore, how this situation – in which the appointments were willingly offered and in which the cancellation was apparently accepted, with good grace, could possibly be interpreted as constituting a breach of Clause 15.4.

PANEL RULING

The Panel noted that the supplementary information to Clause 15.4 of the Code stated that 'Representatives must always endeavour to treat doctors' time with respect and give them no cause to believe that their time might have been wasted. If for any unavoidable reasons, an appointment cannot be kept, the longest possible notice must be given'.

The Panel noted that the two representatives had cancelled appointments with the complainant at short notice. One representative had made her 10am appointment on the day before only to cancel it early in the morning of the day itself with the complainant receiving only two or three hours' notice of the cancellation. The other representative had given the complainant more notice, cancelling her 2pm appointment the day before she was due to visit. Both representatives had been called away by their manager to attend the same meeting. The Panel had no information about this meeting or when the representatives were informed about it. The Panel noted that although the 2pm appointment had been subsequently taken by another Pfizer representative, it appeared that when the original representative cancelled her appointment the complainant had no expectation that another Pfizer representative would take her place.

The Panel noted Pfizer's submission that meetings held at short notice on an *ad hoc* basis were, for the two representatives concerned, relatively frequent occurrences. Given the guidance contained in the supplementary information to Clause 15.4, this was unacceptable. Companies should ensure that they gave their representatives as much notice as possible of forthcoming meetings so that appointments did not need to be cancelled at short notice.

The Panel considered that the period of notice given by the representatives was too short. The event causing the cancellations of the appointments was within the company's control although not within the representatives' control. In the circumstances the Panel ruled no breach of Clause 15.4 but considered that high standards had not been maintained by the company. A breach of Clause 9.1 was ruled.

Complaint received **7 December 2004**

Case completed **11 February 2005**

CASE AUTH/1662/12/04

VOLUNTARY ADMISSION BY MERCK SHARP & DOHME

Breach of undertaking

Merck Sharp & Dohme voluntarily advised the Authority that a journal advertisement ruled in breach of the Code in Case AUTH/1614/8/04 had appeared in Doctor and GP.

The Director of the Authority decided that as the matter related to a potential breach of undertaking it was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This accorded with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

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 future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted from the emails sent between Merck Sharp & Dohme and its agencies that everyone was clear that the advertisements at issue should not be used. Similarly an email from the media buyers to the publications was also clear as to which advertisements must not be used. Recipients were told that any future insertions must be the new advertisement and they were asked to confirm that all old copies had been destroyed.

Letters from GP and Doctor showed that the two publications accepted responsibility for what had happened. The letter from GP acknowledged that it had been asked to destroy all copies containing the claims at issue. Nonetheless advertisements with the strapline previously ruled in breach of the Code had been used. As a consequence of GP and Doctor's actions, Merck Sharp & Dohme had failed to comply with its undertaking and the Panel ruled a breach of the Code.

The Panel considered that the company had been let down by the publications. The company had endeavoured to comply with its undertaking. The Panel did not consider that the company had brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of the Code was ruled including a ruling of no breach of Clause 2.

Merck Sharp & Dohme Limited voluntarily advised the Authority that a claim for Arcoxia (etoricoxib) which had been ruled in breach of the Code in Case AUTH/1614/8/04 had appeared in Doctor and GP on 19 November 2004. Merck Sharp & Dohme had given an undertaking not to use the claim 'Broad range of indications' after 8 October 2004.

The Director of the Authority decided that as the matter related to a potential breach of undertaking it was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This accorded with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review. Merck Sharp & Dohme was asked to respond in relation to Clauses 2, 9.1 and 22 of the Code.

RESPONSE

Merck Sharp & Dohme provided written statements by the two publications which admitted that failings in their internal procedures on the electronic storage of promotional material had led to the error. Merck Sharp & Dohme had been assured that they had since modified their procedures.

Merck Sharp & Dohme considered that it carried out all the relevant actions necessary to comply with the undertaking and these were discharged in good faith. The undertaking was given on 1 October 2004 with confirmation that the advertisement containing the claim 'Broad range of indications' would be published for the last time on 8 October 2004. Merck Sharp & Dohme informed the relevant parties. This involved communication between its marketing department and its media buyer which arranged/booked the advertising space, and liaison with the advertising agency which supplied the 'approved' advertisements to the publications. Every advertisement went through the medical/legal approval system and only when the final proof of each individual advertisement had been signed-off, was it supplied to the publications by the advertising agency.

On the withdrawal of the claim 'Broad range of indications' the following actions were taken to implement the undertaking:

- 24 September: Merck Sharp & Dohme told both the media buyer and the advertising agency that the 'Broad range' strapline was no longer allowed under any circumstance. This was originally by telephone and then email.
- 24 September: All advertising agency employees in contact with the Arcoxia account were similarly told.
- 1 October: The advertising agency told Merck Sharp & Dohme and the media buyer the dates for each publication in which the 'Broad range' strapline was due to be used. This email also stated the instruction to stop publication of any future advertisements even if this meant blank space in the publication.
- 1 October: The media buyer reinforced dates that the 'Broad range' advertisements were due to run and indicated those publications that had already printed and could not withdraw the advertisement – this showed that an advertisement in Update, 8 October would be the final time that the 'Broad range' strapline would run.
- 1 October: e-mail from the media buyer to all publications enforced that the 'Broad range' strapline advertisement must not appear in any publications.
- 1 October: Merck Sharp & Dohme, confirmed internally last date for 'Broad range' was 8 October.

Copies of the emails were provided.

Merck Sharp & Dohme noted that it had told its agencies of the need to withdraw the advertisement at issue and they had passed this information on in writing to the individual publications. However, on 19 November, both GP and Doctor used the 'Broad range' strapline advertisement. Letters provided explained how this error arose at each publication.

Both publications had accepted responsibility for their mistakes and explained the incidents as a combination of human error and the relative inexperience of the individuals involved. Given the additional evidence Merck Sharp & Dohme had provided which supported its assertion that all possible steps were put in place to ensure that it had told its advertising agency and the media-buyers and they had in turn passed on appropriate instructions 'downstream' to comply with the undertaking, Merck Sharp & Dohme did not believe it was culpable for any alleged breach of Clauses 22, 9.1 or 2.

Merck Sharp & Dohme regretted the placement of the wrong advertisement. For the reasons set out above, it believed it had as far as was possible complied with the undertaking (Clause 22); it believed it had maintained high standards throughout this process (Clause 9.1) and would assert that its actions did not in any way justify a finding of bringing discredit to, or reduction of confidence in the industry (Clause 2).

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 future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted from the emails sent between Merck Sharp & Dohme and its agencies that everyone was clear that advertisements using the 'Broad indications' strapline should not be used. Similarly an email from the media buyers to the publications was also clear that advertisements containing the 'Broad indications' strapline must not be used. Recipients were told that any future insertions must be of new copy and they were asked to confirm that all old copies had been destroyed.

Letters from GP and Doctor showed that the two publications accepted responsibility for what had happened. The letter from GP acknowledged that it had been asked to destroy all copies containing the 'Broad range' claims. Nonetheless advertisements with the strapline 'Broad range of indications' had been used. As a consequence of GP and Doctor's actions, Merck Sharp & Dohme had failed to comply with its undertaking and the Panel ruled a breach of Clause 22 of the Code.

The Panel considered that the company had been let down by the publications. The company had endeavoured to comply with its undertaking. The Panel did not consider that the company had brought discredit upon or reduced confidence in the pharmaceutical industry. No breaches of Clauses 9.1 and 2 were ruled.

Proceedings commenced 7 December 2004

Case completed 8 February 2005

COMPANY EMPLOYEE v SCHERING-PLOUGH

ViraferonPeg patient information leaflet

A Schering-Plough employee complained about the company's activities in relation to a draft patient leaflet for ViraferonPeg (peginterferon alfa-2b).

The complainant was extremely concerned that at a team business meeting, representatives were handed a mock-up of a new patient leaflet and asked to visit nurse specialists and consultants to get feedback before the leaflet was printed. The draft patient leaflet did not state 'not to be left with customers' or 'for internal use only'. This information was stated verbally at the meeting together with the fact that the draft leaflet had not been passed through medical and should not be left with clients. This instruction was not written anywhere on the draft leaflet or in subsequent emails. Some people did not hear this instruction and as a result a manager and a representative had been disciplined for allowing a nurse to photocopy and retain the draft leaflet to get feedback from the end user.

The complainant was concerned that: it was a breach of the Code to have representatives whose sole purpose was promotion engaged in pre-marketing research activities; it was in breach because the pre-marketing draft leaflet contained the brand name but no summary of product characteristics (SPC); the company was in breach because the document had not been approved, it was disguised promotion and that it was not stated in writing that the draft leaflet was for pre-marketing research use.

The Panel noted that ViraferonPeg powder and solvent for solution was available in pre-filled pens. The patient had to reconstitute the powder with the solvent before self-injecting. Representatives had been given a copy of a draft patient leaflet which showed how the pen was to be used and listed some frequently asked questions and answers. The representatives were asked to get feedback from nurses and consultants about the suitability of the draft leaflet and to this end were given a list of questions to ask them. Representatives had been told not to leave copies of the draft leaflet with any health professional. One representative had left the draft leaflet with a practice nurse and he and his manager had been disciplined.

The Panel considered that the representatives, in soliciting health professionals' opinions on the draft leaflet, were in effect conducting a market research exercise. Given the involvement of the representatives the Panel considered that the activity came within the scope of the Code but noted that although there were potential conflicts of interest, the Code did not preclude the use of representatives to conduct such research; in that regard the Panel ruled no breach of the Code.

The Panel was unsure whether the draft leaflet was a patient information leaflet (PIL) that was covered by the regulations and needed to be approved before use or whether it was additional to the statutory PIL. The Panel noted that the complainant had alleged a breach of the Code as the draft leaflet did not contain the SPC. Information for patients was not required to contain the SPC or prescribing information as set out in the Code. The Panel thus ruled no breach of the Code in this regard.

The Panel noted the allegation that the draft leaflet had not been passed through the correct medical channels for approval and that as it contained the brand name of the product it was disguised promotion. The Panel noted Schering-Plough's submission that the document was within the approval process. The Panel did not accept that the presence of the brand name on the draft leaflet automatically meant that it was being used as disguised promotion. In that regard the Panel ruled no breach of the Code.

The Panel noted that the complainant had been concerned that it was not stated on the draft leaflet that it was for market research purposes only. Schering-Plough had acknowledged that the leaflet should possibly have been marked with 'Draft', 'For internal use only' or similar. The Panel noted that although representatives had been verbally briefed about how to use the draft leaflet they had not been given any written instructions to reinforce what they had been told. The Panel considered that marking the leaflet with words such as 'Not to be left with customers' would have reinforced the company's wishes and left no room for doubt for either the representatives or health professionals. Nonetheless such statements were not a requirement of the Code and in that regard the Panel ruled no breach of the Code.

An employee of Schering-Plough Ltd complained about the company's activities in relation to a draft patient leaflet for ViraferonPeg (peginterferon alfa-2b).

COMPLAINT

The complainant was extremely concerned that at a team business meeting the team was handed a mock-up document of a new patient leaflet that had not been passed through medical for approval. The original document was provided. Representatives were to visit the nurse specialists and consultants to get feedback before the leaflet was passed by medical and printed.

The complainant noted that the draft leaflet did not state 'not to be left with customers' or 'for internal use only'. This had been verbally stated at the meeting together with the fact that the draft leaflet had not been passed through medical and should not be left with clients. This instruction was not written anywhere on the draft leaflet or in subsequent emails. Because some people in the meeting did not hear this instruction, they were unaware of the importance. As a result of this a manager and a representative had been disciplined for allowing a nurse to photocopy and retain the draft leaflet to get feedback from the end user who would be the intended audience.

The complainant was seriously concerned that: it was a breach of the Code to have representatives whose

sole purpose was promotion engaged in pre-marketing research activities; it was in breach because the pre-marketing draft leaflet contained the brand name but no summary of product characteristics (SPC); the company was in breach because the draft leaflet had not been passed through the correct medical channels for approval as it contained the brand name it was intended for (disguised promotion?) and that it was not stated in writing at any point that the document was for pre-marketing research use.

The complainant believed an investigation was warranted because if any or all of these concerns were correct, then the company put everyone's career at risk by ordering them to carry out their instructions in clear contravention of the rules and regulations.

When writing to Schering-Plough, the Authority asked it to respond in relation to Clauses 2, 9.1, 10.1 and 15.2 of the Code.

RESPONSE

Schering-Plough stated that the document concerned was a draft patient leaflet for a self-injecting pen device. It was not promotional material detailing a medicine. Representatives and managers were given a copy of the leaflet at a briefing meeting and the feedback guide, a copy of which was provided, was emailed to them over the weekend so that they had it on the first working day following the meeting. They were instructed to gain informal feedback from nurses in hospital units they visited on the suitability of the leaflet for patient use by using the guide, but not to issue copies of it under any circumstances: The objective was to get informed feedback before the document was finalized.

Those attending the briefing meeting were instructed on two separate occasions, the second at the beginning of the meeting on the second day, that the draft leaflet had not been finalized and should not therefore be left.

- those attending the meeting were issued with a written guide to be used in soliciting feedback from nurses;
- 14 copies of the document were distributed;
- feedback was to be collected using the guide referred to above.

It was made very clear at the briefing meeting that the draft leaflet was not to be issued.

Subsequently the company learned, by means of an internal email from a representative to head office that a copy of the unapproved draft leaflet had been left with a practice nurse. The reply to the representative stated that it had been made clear at the briefing that the draft leaflet was not to be left with customers and that it should be immediately recovered.

The representative concerned had asked his manager, who happened to be present, if he could ignore the instruction and provide a photocopy to a nurse, and his manager agreed to this. When this came to light the company invoked its disciplinary procedure in the case of both employees.

Addressing the alleged breaches of the Code, the objective of the exercise in question was to validate a patient education leaflet which set out the technique of using a self-injection pen. Indeed the exercise was designed to gain expert views on the item, thus improving patient care. The sales team was asked to show the draft leaflet to some of the nurses and then feedback their views to the product manager using the guide.

Schering-Plough did not consider that this was a market research exercise or that the draft leaflet was promotional. However, in keeping with its current procedure this draft leaflet was within the approval process which was initiated two days before the representatives' briefing meeting. Schering-Plough thus believed it was appropriate for the sales team to validate the item. The draft leaflet was designed to instruct patients how to use the pen delivery system for ViraferonPeg which they had been prescribed.

Schering-Plough considered that asking representatives to seek the views of nurses on such aids did not breach the Code. The document simply gave instructions on how to prepare and use the pen and sought to deal with problems which might arise during its use. It did not make any promotional claims.

Schering-Plough did not consider these activities to be a breach of Clause 2.

Carrying out this validation exercise was aimed at creating the best possible patient education document. Schering-Plough did not consider that this exercise was a breach of Clause 9.1. The item in question was a patient education leaflet designed to help those who had been prescribed the product. The feedback form showed clearly that the objective was not to disguise promotion of the product. Therefore there was no breach of Clause 10.1.

Representatives were given clear oral instructions as to the use of the draft leaflet and that on no account should it be left with any health professionals. This instruction was ignored by the manager and one of his representatives. Indeed, the representative made it clear in an email to head office that he had heard the instruction. Schering-Plough provided copies of the relevant emails.

Schering-Plough submitted that it and its representatives had maintained a high standard of ethical conduct and had not breached Clause 15.2.

With hindsight, this leaflet should possibly have been marked with 'Draft', 'For internal use only' or some other such marking and the relevant policy would be amended to include this provision in future.

PANEL RULING

The Panel noted that ViraferonPeg powder and solvent for solution was available in pre-filled pens. The patient had to reconstitute the powder with the solvent before self-injecting. Representatives had been given a copy of a draft patient leaflet which showed how the pen was to be used and listed some frequently asked questions and answers. The representatives were asked to get feedback from

nurses and consultants about the suitability of the draft leaflet and to this end were given a list of questions to ask them. Representatives had been told not to leave copies of the draft leaflet with any health professional. One representative had left the leaflet with a practice nurse and he and his manager had been disciplined.

The Panel considered that the representatives, in soliciting health professionals' opinions on the draft leaflet, were in effect conducting a market research exercise. The supplementary information to Clause 10.2 stated, *inter alia*, that market research must be unbiased and non-promotional. Given the involvement of the representatives the Panel considered that the activity came within the scope of the Code but noted that although there were potential conflicts of interest, the Code did not preclude the use of representatives to conduct such research; in that regard the Panel ruled no breach of Clauses 2, 9.1 and 15.2.

The Panel was unsure whether the draft leaflet was a patient information leaflet (PIL) that was covered by the regulations and needed to be approved before use or whether it was additional to the statutory PIL. The Panel noted that the complainant had alleged that the draft leaflet was in breach of the Code because it did not contain the SPC. Information for patients was not required to contain the SPC or prescribing information as set out in Clause 4.1 of the Code. The Panel thus ruled no breach of Clause 9.1 of the Code in this regard.

The Panel noted that the complainant had alleged that the draft leaflet had not been passed through the correct medical channels for approval and that as it contained the brand name of the product it was disguised promotion. The Panel noted Schering-Plough's submission that the document was within the approval process. Clause 10.2 of the Code stated that market research activities must not be disguised promotion. The supplementary information to Clause 10.2 drew attention to The Legal and Ethical Framework for Healthcare Market Research produced by the British Healthcare Business Intelligence Association in consultation with the Association of the British Pharmaceutical Industry. The Panel did not accept that the presence of the brand name on the draft leaflet automatically meant that it was being used as disguised promotion. In that regard the Panel ruled no breach of Clauses 9.1 and 10.2 of the Code.

The Panel noted that the complainant had been concerned that it was not stated on the draft leaflet that it was for market research purposes only. Schering-Plough had acknowledged that the material should possibly have been marked with 'Draft', 'For internal use only' or similar. The Panel noted that although representatives had been verbally briefed about how to use the draft leaflet they had not been given any written instructions to reinforce what they had been told. They did not appear to have been given any verbal or written instruction on the non-promotional nature of the exercise. Given that market research was not a usual task for representatives it would have been helpful for them to have had some written guidance. The Panel further considered that it would have been helpful to have marked the leaflet itself such that it was clear to everyone that it was still just a draft although in that regard the Panel noted that as provided the leaflet still had the printer's marks on the edges; it was clearly not a final document. Marking the leaflet with words such as 'Not to be left with customers' would, however, have reinforced the company's wishes to its representatives and left no room for doubt for either the representatives or health professionals. Nonetheless such statements were not a requirement of the Code and in that regard the Panel ruled no breach of Clause 9.1 of the Code.

Complaint received **13 December 2004**

Case completed **14 February 2005**

CASE AUTH/1665/12/04

GENERAL PRACTITIONER v ASTRAZENECA

Announcement of a price reduction for Zoladex, Arimidex and Nexium

A general practitioner complained that in a four page letter sent by AstraZeneca, announcing price reductions for Zoladex, Arimidex and Nexium, and giving their respective indications, the approved names were not stated immediately adjacent to the most prominent displays of the three brand names. The prescribing information was given on a separate piece of paper.

The Panel considered that the letter was an advertisement. It included brand names and indications. The Panel noted that the relevant non-proprietary names did not appear immediately adjacent to the most prominent displays of the brand names, Zoladex, Arimidex and Nexium. A breach of the Code was ruled. The pages of the letter were stapled together and numbered such that it was obvious that the whole letter consisted of four pages. The prescribing information was on pages numbered 3/4 and 4/4 and was thus an integral part of the letter. No breach of the Code was ruled.

A general practitioner complained about a four page letter (ref AZ-11/04-15076) from AstraZeneca UK Limited which informed recipients of price reductions for Zoladex, Arimidex and Nexium and stated their respective indications. Page 2 gave the references and the prescribing information for Arimidex, Zoladex and Nexium was given on pages 3 and 4.

COMPLAINT

The complainant stated that the letter could be in breach of the Code. It announced the welcome news that NHS prices had been reduced. For the three products mentioned, Zoladex, Arimidex and Nexium, the approved name was not mentioned adjacent to the most prominent display of the brand names. A separate sheet was enclosed containing prescribing information for the three products and so AstraZeneca presumably considered this to be a promotional exercise as well as an announcement of information.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 4.1 and 4.3 of the Code.

RESPONSE

AstraZeneca stated that the letter in question was an announcement about three AstraZeneca brands, the prices of which had been reduced in 2005 as a result of the Pharmaceutical Price Regulation Scheme (PPRS). Since the letter also contained some information on the brands mentioned, prescribing information was included.

The letter was sent out to all GPs (including dispensing GPs), practice managers, hospital clinical directors, primary care trust (PCT) prescribing advisers and finance directors and retail pharmacists on 29 November 2004.

AstraZeneca accepted that the non-proprietary names did not appear adjacent to the most prominent display of the brand names. AstraZeneca also noted that the prescribing information appeared on separate pages. These were errors and AstraZeneca apologised for this oversight.

PANEL RULING

The Panel considered that the letter was an advertisement. It included brand names and indications. The relevant non-proprietary names did not appear immediately adjacent to the most prominent displays of the brand names, Zoladex, Arimidex and Nexium on page 1 of the letter. The Panel ruled a breach of Clause 4.3 of the Code as acknowledged by AstraZeneca.

The Panel noted that the four, single sided pages of the letter were stapled together. The pages were numbered such that it was clear that the whole letter consisted of four pages. The prescribing information appeared on pages numbered 3/4 and 4/4. The prescribing information was thus an integral part of the letter. The Panel ruled no breach of Clause 4.1 of the Code in this regard.

Complaint received **13 December 2004**

Case completed **21 January 2005**

CASE AUTH/1666/12/04 *NO BREACH OF THE CODE*

JANSSEN-CILAG/DIRECTOR v NAPP

Promotion of Transtec

Janssen-Cilag complained about claims for low potency in a mailing and leavepiece for Transtec (buprenorphine transdermal patch) issued by Napp. Janssen-Cilag supplied Durogesic (fentanyl transdermal patch).

As the complaint involved an alleged breach of undertaking that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Code of Practice Appeal Board.

Janssen-Cilag noted that in its complaint (Case AUTH/1591/5/04) the Panel had ruled breaches of the Code as Napp had misleadingly claimed that 'Transtec matrix patches can be used sooner than fentanyl reservoir patches' and that 'Transtec's low starting dose means that it might be appropriate to use before fentanyl in strong opioid naïve patients'. It was additionally noted that Durogesic was licensed for use in patients who had not previously received a strong opioid.

Janssen-Cilag was disappointed to see a 'low potency' claim in that Transtec's lowest strength patch apparently had a lower potency than Durogesic's lowest strength patch. The claims were referenced to the respective summaries of product characteristics (SPCs). Janssen-Cilag had, however, not found any reference to potency within the SPCs. The claim at issue implied that there might be a group of patients for whom Transtec could be prescribed where Durogesic might be too strong. This was not the case, as evidenced by the respective SPCs, and was further confirmed by the Panel's ruling in Case AUTH/1591/5/04.

Janssen-Cilag believed that no practical advantage had been demonstrated within the promotional items and the references used. Janssen-Cilag noted Napp's comment that clear instructions had been given to the Napp sales force in that Transtec patches could not be used before Durogesic. It seemed therefore that any claims of potency from a clinical perspective (as within the promotional items) were completely irrelevant.

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 future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted its ruling in Case AUTH/1591/5/04 that according to their respective SPCs the lowest strength Transtec patch (35µg/h) was equivalent to 30-60mg oral morphine per day, and the lowest strength Durogesic patch (25µg/h) was equivalent to oral doses of morphine of less than 135mg/day. Under the heading dose titration the Durogesic SPC stated that Durogesic 25µg/h was approximately equivalent to 90mg/day of oral morphine. The Panel acknowledged that there was a difference between the products in that the lowest strength Transtec patch was less potent than the lowest strength Durogesic patch. The Transtec SPC indicated that the product could be used in patients who had previously not received any analgesics whereas the Durogesic SPC stated that the initial dose should be based, *inter alia*, on the patient's opioid history. The Panel noted, however, that both the detail aid and the leavepiece referred, on their front covers, to Transtec as 'Your next step after a weak opioid in severe, chronic pain' and it was in this context that the claims at issue were considered.

Both the detail aid and the leavepiece stated that 'Transtec matrix patches can be used sooner than [Durogesic] patches', followed by a description of the oral morphine equivalent of the lowest strength of both products, followed by the claim 'Trantec's low starting dose means it may be appropriate to use before [Durogesic] in strong opioid naïve patients'.

Durogesic 25µg/h was licensed for use in patients who had not previously received a strong opioid. This was not made sufficiently clear in the materials. The Panel noted that the claim stated that Transtec 'may be appropriate to use before [Durogesic]' but considered that use of the word 'may' did not negate the impression that Transtec was appropriate to use before Durogesic. Given the licensed indications for both products with regard to patients who needed more than a weak opioid, the Panel considered that, in the context in which they appeared, the claims 'Transtec matrix patches can be used sooner than fentanyl reservoir patches' and 'Transtec's low starting dose means that it may be appropriate to use before fentanyl in strong opioid naïve patients' were misleading and could not be substantiated. Breaches of the Code were ruled. The Panel further considered that the claims disparaged Durogesic. A breach of the Code had been ruled.

In the present case, Case AUTH/1666/12/04, the Panel considered that the claim that 'The lowest strength Transtec patch is less potent than the lowest strength fentanyl patch' was sufficiently different to the claims previously at issue 'Transtec matrix patches can be used sooner than fentanyl reservoir patches' and 'Transtec's low starting dose means that it may be appropriate to use before fentanyl in strong opioid naïve patients' for there not to have been a breach of undertaking. The Panel thus ruled no breach of the Code.

The leavepiece included a page headed 'Transtec and fentanyl potency comparison' followed by the claim at issue and a chart depicting the lowest patch strengths for Transtec and fentanyl with their equivalent oral morphine doses in a 24 hour period (30-60mg vs up to 135mg respectively).

The Panel noted that the claim at issue was for inferior potency. The relevant SPCs did not mention potency *per se* but did give information about equivalent oral morphine doses for each patch. The relevant data in the Transtec SPC was referred to as a 'rough guideline'. The relevant data in the Durogesic SPC was referred to as a 'recommended

conversion scheme from oral morphine to Durogesic' and that oral morphine 90mg/day was approximately equal to Durogesic 25µg/h.

The Panel considered that there was a practical advantage for the lowest dose Transtec patch in that the equivalent oral morphine dose of 30-60mg/day was less than the lowest dose fentanyl patch equivalent oral morphine dose of 90-<135mg/day.

The Panel did not consider that the claim in the leavepiece implied that Transtec could be used sooner than fentanyl patch as alleged and ruled no breach of the Code.

The mailing also included the claim at issue 'The lowest strength Transtec patch is less potent than the lowest strength fentanyl patch', referenced to the two SPCs. Unlike the leavepiece, however, no information regarding oral morphine equivalent doses was given in the mailing. Nonetheless, the Panel considered that its comments regarding the leavepiece were relevant. The Panel did not consider that the claim implied that the lowest dose Transtec patch could be used sooner than the lowest dose fentanyl patch as alleged; no breach of the Code was ruled.

Janssen-Cilag Ltd complained about the promotion of Transtec (buprenorphine transdermal patch) by Napp Pharmaceuticals Limited. The items at issue were a mailer (ref UK/TR-04534) and a leavepiece (ref UK/TR-04536). Inter-company communications had failed to resolve the matter. Janssen-Cilag supplied Durogesic (fentanyl transdermal patch).

As the complaint involved an alleged breach of undertaking that aspect was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Code of Practice Appeal Board.

COMPLAINT

Janssen-Cilag alleged breaches of Clauses 2, 7.2 and 22 of the Code with regard to the use of a claim for low potency.

Janssen-Cilag noted that the Authority had recently upheld its complaint about claims made by Napp for Transtec (Case AUTH/1591/5/04). In that case the Panel ruled breaches of Clauses 7.2 and 7.4 in that Napp had misleadingly claimed that 'Transtec matrix patches can be used sooner than fentanyl reservoir patches' and that 'Transtec's low starting dose means that it might be appropriate to use before fentanyl in strong opioid naïve patients'. It was additionally noted that Durogesic was licensed for use in patients who had not previously received a strong opioid.

Given this background, Janssen-Cilag was more than surprised and very disappointed to note the use of a 'low potency' claim in Napp's two promotional items in that Transtec's lowest strength patch apparently had a lower potency than Durogesic's lowest strength patch. The claims in both items were referenced to the respective summaries of product characteristics (SPCs). Janssen-Cilag had, however, not found any reference to potency within the SPCs.

Janssen-Cilag's main concern was that the claim implied that there might be a group of patients for whom Transtec could be prescribed where Durogesic might be too strong. This was not the case, as evidenced by the respective SPCs, and was further confirmed by the Panel's ruling.

Janssen-Cilag noted that, *inter alia*, the supplementary information to Clause 7.2 very clearly and specifically stated that claims for superior potency were generally meaningless unless they could be linked with some practical advantage. Janssen-Cilag alleged that no practical advantage had been demonstrated within the promotional items and the references used. Janssen-Cilag noted that Napp had stated that clear instructions had been given to its sales force in that Transtec patches could not be used before Durogesic. It seemed therefore that any claims of potency from a clinical perspective (as was being used within the promotional items) were completely irrelevant.

Janssen-Cilag alleged there was a repeated breach of Clause 7.2 regarding the use of the low potency claim, and a breach of undertaking (Clause 22) from Case AUTH/1591/5/04. Given that breaches of undertaking brought clear discredit upon the industry, Janssen-Cilag also alleged a breach of Clause 2.

RESPONSE

Napp submitted that the claim at issue 'The lowest strength Transtec patch is less potent than the lowest strength fentanyl patch', was different from those at issue in Case AUTH/1591/5/04, 'Transtec patches can be used sooner than fentanyl patches' and 'Transtec's lower starting dose means that it may be appropriate to use before fentanyl in strong opioid naïve patients'.

The claim was based on the morphine equivalence data contained in the SPCs. The Durogesic SPC stated that the lowest strength Durogesic patch (25µg/h) was equivalent to oral doses of morphine of up to 135mg/day, whilst the Transtec SPC stated that the lowest strength patch (35µg/h) was equivalent to oral doses of morphine of between 30-60mg/day. As the Transtec patch 35µg/h was equivalent to a lower oral dose of morphine per day than the Durogesic patch 25µg/h, it was therefore less potent than the lowest strength Durogesic patch.

Napp submitted that its current claim reflected the Panel's ruling in Case AUTH/1595/5/04 wherein the Panel acknowledged there was a difference between the products in that the lowest strength Transtec patch was less potent than the lowest strength Durogesic patch. Napp considered that its claim of less potency was therefore consistent with both products' SPCs and the Panel's decision.

Unlike the claims at issue in Case AUTH/1595/5/04, the claim now at issue did not suggest that there might be patients for whom Transtec could be prescribed where Durogesic might be inappropriate. Napp had simply highlighted the relative morphine equivalence as stated in the two SPCs, and it was up to the prescriber as to what weight to give this information when making prescribing decisions.

Napp noted that a recent letter underscored the importance and clinical relevance of educating doctors on the relative potency of transdermal products (Botterman *et al* 2004). The authors described a retrospective study involving the case notes of 460 patients admitted to a Belgian palliative care unit during 1999-2001. Among the patients receiving major analgesics on admission, equal numbers were receiving oral morphine and transdermal fentanyl. However, patients receiving fentanyl were on a substantially higher median dose (270mg oral morphine equivalent) than those receiving morphine (60mg). The difference in dosage could not be explained by the fact that those on fentanyl were suffering from more pain than the other patients. The authors noted that a number of patients on fentanyl were clearly intoxicated at admission, and the medicine needed to be reduced or stopped in a number of patients due to excessive toxicity or inappropriate dose level. The authors stated, 'Contrary to the reticence many doctors and patients still feel towards the use of morphine, practitioners do not always appreciate the dose-equivalence of the fentanyl patches and may on some occasions be using the drug inappropriately and at much higher doses than they would risk using oral or parenteral morphine'.

Furthermore, in view of Janssen-Cilag's insistence that there were no patients in which Transtec 35µg/h could be used before Durogesic 25µg/h, Napp noted that the company had recently launched a lower strength fentanyl patch in Germany, which it believed would soon be launched in the UK. The new Durogesic SMAT 12µg/h was approximately half the strength of the previous lowest dose of Durogesic, with an oral morphine equivalence of 30-45mg/day. This raised the obvious question that if the Durogesic 25µg/h patch was equivalent to 0-135mg/day of oral morphine, then why introduce a 12µg/h Durogesic patch? For what group of patients was this lower strength appropriate? It also seemed inconsistent that the Durogesic 25µg/h patch was stated to be equivalent to 0-135mg of oral morphine per day, whilst the Durogesic 12µg/h patch was stated to be equivalent to 30-45mg of morphine per day.

In summary, the claim that the lowest strength Transtec patch was less potent than the lowest strength Durogesic patch was a statement of fact, based on the morphine equivalence set out in both products' SPCs, which was of practical use to prescribers. It was not the same as claiming that Transtec might be used earlier than Durogesic, as in Napp's previous materials. There was evidence, Botterman *et al*, that doctors were unaware of the daily oral morphine equivalence of opioid patches, and it was in both doctors' and patients' interests that this was clarified. Accordingly, Napp submitted that highlighting the relative potency of Transtec and Durogesic patches conveyed information that was of practical benefit to prescribers and did not breach Clause 7.2.

With regard to the alleged breach of undertaking, Napp had understood the Panel's ruling to mean that it could not claim that Transtec could be used sooner than Durogesic. Transtec materials used after the ruling in Case AUTH/1591/5/04 did not claim this, so Napp had fully complied with this undertaking. Napp also understood it could claim that the lower strength Transtec patches were less potent than the lowest strength Durogesic patch, and the undertaking was given on this basis. The revised Transtec materials made precisely this claim, ie 'The lowest strength Transtec patch is less potent than the lowest strength fentanyl patch'. Napp denied a breach of Clause 22 and refuted the allegation that it had brought discredit upon the industry in breach of Clause 2 of the Code.

Napp stated that on the same day as it gave its undertaking in Case AUTH/1591/5/04 it also gave clear instructions in an email to its entire sales and marketing department, requesting the immediate withdrawal of all Transtec materials containing the claims that were ruled in breach of the Code.

The email also confirmed that the claims at issue should no longer be made in any written or verbal communication to health professionals and required the destruction of these materials to be verified in accordance with company procedures.

Napp stated that as it promptly withdrew and destroyed the materials ruled to be in breach of the Code and its new Transtec materials complied with its undertaking and did not include the above claims, it did not see any basis upon which its actions could be viewed as bringing discredit upon the industry in breach of Clause 2.

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 future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted its ruling in Case AUTH/1591/5/04.

Case AUTH/1591/5/04

The Panel noted that according to its SPC the lowest strength Transtec patch (35µg/h) was equivalent to 30-60mg oral morphine per day. The lowest strength Durogesic patch (25µg/h) was equivalent to oral doses of morphine of less than 135mg/day according to part of Section 4.1 of its SPC. Under the heading dose titration the SPC stated that Durogesic 25µg/h was approximately equivalent to 90mg/day of oral morphine. The Panel acknowledged that there was a difference between the products in that the lowest strength Transtec patch was less potent than the lowest strength Durogesic patch. The Transtec SPC indicated that the product could be used in patients who had previously not received any analgesics whereas the Durogesic SPC stated that the initial dose should be based, *inter alia*, on the patient's opioid history. The Panel noted, however, that both the detail aid and the leavepiece referred, on their front covers, to Transtec as 'Your next step after a weak opioid in severe, chronic pain' and it was in this context that the claims at issue were considered.

Both the detail aid and the leavepiece stated that 'Transtec matrix patches can be used sooner than

[Durogesic] patches', followed by a description of the oral morphine equivalent of the lowest strength of both products, followed by the claim 'Trantec's low starting dose means it may be appropriate to use before [Durogesic] in strong opioid naïve patients'.

Durogesic 25µg/h was licensed for use in patients who had not previously received a strong opioid. This was not made sufficiently clear in the materials. The Panel noted that the claim stated that Transtec '**may** (emphasis added) be appropriate to use before [Durogesic]' but considered that use of the word 'may' did not negate the impression that Transtec was appropriate to use before Durogesic. Given the licensed indications for both products with regard to patients who needed more than a weak opioid, the Panel considered that, in the context in which they appeared, the claims 'Transtec matrix patches can be used sooner than fentanyl reservoir patches' and 'Transtec's low starting dose means that it may be appropriate to use before fentanyl in strong opioid naïve patients' were misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled. The Panel further considered that the claims disparaged Durogesic. A breach of Clause 8.1 was ruled.

Case AUTH/1666/12/04

The Panel considered that the claim that 'The lowest strength Transtec patch is less potent than the lowest strength fentanyl patch' was sufficiently different to the claims previously at issue 'Transtec matrix patches can be used sooner than fentanyl reservoir patches' and 'Transtec's low starting dose means that it may be appropriate to use before fentanyl in strong opioid naïve patients' for there not to have been a breach of undertaking. The Panel thus ruled no breach of Clause 22 of the Code. Consequently no breach of Clause 2 was also ruled.

Turning to the alleged breach of Clause 7.2, the leavepiece included a page headed 'Transtec and fentanyl potency comparison' followed by the claim at issue and a chart depicting the lowest patch strengths for Transtec and fentanyl with their equivalent oral morphine doses in a 24 hour period (30-60mg vs up to 135mg respectively).

The Panel noted that the supplementary information to Clause 7.2 referred to claims for superior potency. The claim at issue was for inferior potency. The relevant SPCs did not mention potency *per se* but did give information about equivalent oral morphine doses for each patch. The relevant data in the Transtec SPC was referred to as a 'rough guideline'. The relevant data in the Durogesic SPC was referred to as a 'recommended conversion scheme from oral morphine to Durogesic' and that oral morphine 90mg/day was approximately equal to Durogesic 25µg/h.

The Panel considered that there was a practical advantage for the lowest dose Transtec patch in that the equivalent oral morphine dose of 30-60mg/day was less than the lowest dose fentanyl patch equivalent oral morphine dose of 90-<135mg/day.

The Panel did not consider that the claim in the leavepiece implied that Transtec could be used sooner than fentanyl patch as alleged and thus ruled no breach of Clause 7.2 of the Code.

The mailing also included the claim at issue 'The lowest strength Transtec patch is less potent than the lowest strength fentanyl patch', referenced to the two SPCs. Unlike the leavepiece, however, no information regarding oral morphine equivalent doses was given in the mailing. Nonetheless, the Panel considered that its comments regarding the leavepiece were relevant. The Panel did not consider that the claim implied that the lowest dose Transtec patch could be used sooner than the lowest dose fentanyl patch as alleged; no breach of Clause 7.2 of the Code was ruled.

Complaint received **14 December 2004**

Case completed **18 February 2005**

CASE AUTH/1668/12/04 *NO BREACH OF THE CODE*

PRIMARY CARE TRUST HEAD OF MEDICINES MANAGEMENT v PFIZER

Depo-Provera 'Dear Healthcare Professional' letter

The head of medicines management at a primary care trust alleged that a 'Dear Healthcare Professional' letter, sent by Pfizer, was misleading with regard to the prescribing advice about Depo-Provera (medroxy progesterone acetate injectable suspension) recently issued by the Committee on Safety of Medicines (CSM). The CSM advice read 'In women with significant lifestyle and/or medical risk factors for osteoporosis other methods of contraception should be considered'. Pfizer, however, had added '… prior to the use of Depo-Provera' to the end of the sentence.

The Panel noted that following a review of the data by the CSM new prescribing advice for Depo-Provera had been issued, the summary of product characteristics (SPC) had been revised and letters had been sent to health professionals from Pfizer and the CSM. Emails showed that Pfizer and the Medicines and Healthcare products Regulatory Agency (MHRA) had co-operated over the wording of both the SPC and the letter at issue. The letter from Pfizer started with 'Pfizer Ltd would like to inform you of important updated safety information for Depo-Provera following a review of the available data by the [CSM]'. In the Panel's view the letter thus referred to the CSM's review of the data but not to the guidance which it had issued *per se*.

The Panel noted that the statement at issue in the letter 'In women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered prior to use of Depo-Provera' also appeared in the SPC. The SPC represented the agreed information about a product. Given the context in which it was presented the Panel did not consider that the statement in the letter was misleading as alleged. No breach of the Code was ruled.

The head of medicines management at a primary care trust complained about a 'Dear Healthcare Professional' letter about Depo-Provera (medroxyprogesterone acetate injectable suspension) sent by Pfizer Limited. The letter had been sent to practicing general practitioners, obstetrics and gynaecology practitioners and family planning clinics.

COMPLAINT

The complainant stated that on 18 November the Committee on Safety of Medicines (CSM) issued updated prescribing advice on the use of Depo-Provera, a copy of which was provided.

Pfizer had written to health professionals about the matter. Under 'Key Messages' the letter purported to represent the CSM's recommendations but the wording had been changed from the original. The CSM advice read: 'In women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered'. Pfizer, however, had added '… prior to use of Depo-Provera' to the end of the sentence.

The complainant alleged that the letter was misleading.

When writing to Pfizer, the Authority asked it to comment in relation to Clause 7.2 of the Code.

RESPONSE

Pfizer submitted that the sentence at issue was quoted directly from Section 4.4 of the newly revised (18 November 2004) Depo-Provera summary of product characteristics (SPC).

The letter and the new wording on the SPC were agreed through discussions, supported by correspondence, with the Medicines and Healthcare products Regulatory Agency (MHRA) during which the MHRA approved the final version of the letter. Copies of the correspondence were provided.

In summary, Pfizer did not accept that the letter was in breach of the Code. It was agreed with the MHRA and it quoted directly and appropriately from the Depo-Provera SPC. Pfizer could not explain the omission of the words '… prior to use of Depo-Provera' from the CSM advice.

PANEL RULING

The Panel noted that following a review of the data by the CSM new prescribing advice for Depo-Provera had been issued. This had resulted in a revision of the SPC and letters being sent to health professionals from Pfizer and the CSM. Emails showed that Pfizer and the MHRA had co-operated over the wording of both the SPC and the letter at issue. The letter from Pfizer opened with the sentence 'Pfizer Ltd would like to inform you of important updated safety information for Depo-Provera following a review of the available data by the [CSM]'. In the Panel's view the letter thus referred to the CSM's review of the data but not to the guidance which it had issued *per se*.

The Panel noted that the statement at issue in the letter 'In women with significant lifestyle and/or medical risk factors for osteoporosis, other methods of contraception should be considered prior to use of Depo-Provera' also appeared in Section 4.4 of the SPC. The SPC represented the agreed information about a product. Given the context in which it was presented the Panel did not consider that the statement in the letter was misleading as alleged. No breach of Clause 7.2 was ruled.

Complaint received **22 December 2004**

Case completed **16 February 2005**

GENERAL PRACTITIONER v LILLY and BOEHRINGER INGELHEIM

Yentreve referral summary sheet

A general practitioner complained about a Yentreve (duloxetine) referral summary sheet distributed by Lilly and Boehringer Ingelheim. Yentreve was indicated for the treatment of moderate to severe stress urinary incontinence (SUI) in women. The summary sheet gave details about Yentreve on the front and a suggested SUI algorithm and prescribing information on the reverse.

The complainant stated that Yentreve was a selective serotonin and noradrenaline reuptake inhibitor (SNRI) exactly like venlafaxine; the Internet showed that it was marketed in the US as an antidepressant with direct comparisons to venlafaxine in clinical trials. Materials in the UK, however, did not mention any antidepressant action, nor the possibility of a withdrawal syndrome. The complainant was concerned that without this information, Yentreve might be inappropriately prescribed.

The Panel noted that when the referral summary sheet was used, duloxetine was not licensed for the treatment of major depressive disorder. Cymbalta (duloxetine) was granted a marketing authorization for this indication in December 2004.

The referral summary sheet gave details of discontinuation of treatment and stated in bold in a section entitled 'Pharmacological properties' that duloxetine was a combined SNRI. The prescribing information advised caution if used concomitantly with serotonergic antidepressants with venlafaxine given as an example. Caution was also advised in patients with a history of mania, and isolated cases of suicidal ideation or behaviours had been reported; patients were to be encouraged to report any distressing thoughts or feelings.

The Panel did not consider that it was misleading not to mention antidepressant activity in the item at issue; if it had the companies might have promoted an unlicensed indication which was prohibited by the Code. The front of the item and the prescribing information referred to discontinuation of treatment. The Panel did not consider that the failure to refer to withdrawal symptoms was misleading. The material was consistent with the SPC by referring to discontinuation of treatment. The Panel ruled no breach of the Code.

A general practitioner complained about an A5 Yentreve (duloxetine) referral summary sheet (ref SUI261 September 2004). The sheet bore the logos of both Eli Lilly and Company Limited and Boehringer Ingelheim Limited and was distributed by secondary care representatives.

Yentreve was indicated for the treatment of moderate to severe stress urinary incontinence (SUI) in women. The summary sheet gave details about Yentreve on the front and a suggested SUI algorithm and prescribing information on the reverse.

COMPLAINT

The complainant stated that Yentreve was a selective serotonin and noradrenaline reuptake inhibitor (SNRI) exactly like venlafaxine; the Internet showed that it was marketed in the US as an antidepressant with direct comparisons to venlafaxine in clinical trials.

The UK marketing for Yentreve did not mention any antidepressant action, nor that there might be a withdrawal syndrome. The complainant had seen several patients with venlafaxine who had had quite acute withdrawal syndromes and knew of a patient, already taking venlafaxine, who was prescribed Yentreve by a hospital unit which was completely unaware of the potential problems.

The complainant believed that the company responsible might be seeking a marketing licence as an antidepressant as well, but there were many potential dangers here – for instance a patient who was known to have mental illness, perhaps with occasional suicidal idealisation or with mania, might be prescribed it by a doctor unaware (without reading the small print carefully) that this was a very dangerous thing to do.

The Authority asked both Lilly and Boehringer Ingelheim to comment in relation to Clauses 7.2 and 7.9 of the Code.

RESPONSE

Lilly and Boehringer Ingelheim submitted a joint response.

The material at issue was from a referral summary note pad of duplicate sheets of information about Yentreve which could be torn off a page at a time and sent with a letter from the consultant back to the referring GP to provide more information about the product. As Yentreve had only recently become available this pad was provided to specialists (urologists, gynaecologists, uro-gynaecologists) to aid knowledge and understanding of Yentreve by the referring GPs.

The companies submitted that the material at issue was supplementary information to the correspondence normally provided by specialists when referring patients to primary care. It was not intended to substitute normal correspondence and it was the consultant who decided whether to send this to the GP. Each page included prescribing information in a prominent position.

The companies stated that most of the information was taken from the summary of product characteristics (SPC), with the exception of the

suggested algorithm and the efficacy statement. The positioning of Yentreve in the suggested algorithm was in line with the SPC and had been placed into clinical context. The first efficacy statement was derived from the registration trial data; the second statement was derived from the SPC but tailored to meet the requirements of the Code. The adverse events listed were those seen with an incidence of >5% in the Yentreve clinical trials and further information on side-effects was available within the prescribing information.

Yentreve was an SNRI and this was clearly stated in bold font under 'Pharmacological properties'. This product was not 'exactly' like venlafaxine as they had different pharmacokinetic and pharmacodynamic profiles. Yentreve was licensed for women with moderate to severe SUI and, at the time of writing the material at issue (and at the time of the subsequent launch of Yentreve), duloxetine was not licensed for major depressive disorder in the UK. Therefore the companies had not mentioned the use of duloxetine as an antidepressant as this could have been interpreted as pre-licence promotion of this indication and thus in breach of the Code and UK legislation. The companies had endeavoured at all times to promote good clinical practice, informing physicians of relevant information without contravening the Code by disclosing a pending indication.

The 'Dosage & formulation' section on the front of the referral sheet clearly stated that Yentreve should be tapered upon discontinuation of treatment. This recognised the potential health risk of discontinuation symptoms which were also described in the prescribing information.

The companies stated that the prescribing information was the minimum information that should be understood before a product was prescribed. The prescribing information clearly stated under the heading 'Interactions' that caution was advisable if duloxetine was prescribed with venlafaxine. It was not given as a contraindication. In addition, suicidal ideation and mania were both clearly mentioned in the prescribing information as precautions.

Duloxetine (Cymbalta) had been granted a marketing authorization on 17 December 2004 for the treatment of major depressive disorder and the product would be made available for this indication shortly. The companies were aware that there was a potential for confusion regarding the two indications of duloxetine. When duloxetine was launched for major depressive disorder, information would be made available to health professionals regarding the two indications and their dosing regimens. The companies were also working with prescribing software providers to minimise this potential for confusion.

In conclusion the companies denied that the referral summary sheet was in breach of Clauses 7.2 or 7.9 of the Code.

PANEL RULING

The Panel noted that at the time the referral summary sheet was used, duloxetine was not licensed for the treatment of major depressive disorder. Cymbalta (duloxetine) had been granted a marketing authorization for this indication in December 2004.

The referral summary sheet gave details of discontinuation of treatment and stated in bold in a section entitled 'Pharmacological properties' that duloxetine was a combined serotonin and noradrenaline reuptake inhibitor. The prescribing information advised caution if used concomitantly with serotonergic antidepressants with venlafaxine given as an example. Caution was also advised in patients with a history of mania, and isolated cases of suicidal ideation or behaviours had been reported; patients were to be encouraged to report any distressing thoughts or feelings.

The Panel did not consider that it was misleading not to mention antidepressant activity in the item at issue; if it had the companies might have promoted an unlicensed indication which was prohibited by Clause 3 of the Code. The front of the item and the prescribing information referred to discontinuation of treatment. The Panel did not consider that the failure to refer to withdrawal symptoms was misleading. The material was consistent with the SPC by referring to discontinuation of treatment. The Panel ruled no breach of Clauses 7.2 and 7.9 of the Code.

Complaint received **23 December 2004**

Case completed **18 February 2005**

CASE AUTH/1675/1/05

HOSPITAL NHS FOUNDATION TRUST v NAPP

Conduct of a representative

The secretary of a hospital NHS foundation trust complained that a representative from Napp had used the trust's internal email system to promote Oxynorm to anaesthetists.

The Panel noted that the email sent by the representative referred to a diamorphine shortage and the availability and use of OxyNorm injection as an alternative in moderate to severe post-operative pain. The representative had, in effect, written her own piece of promotional material.

The Panel considered that the representative's actions were totally unacceptable; there appeared to be a serious lack of understanding of the requirements of the Code. The trust's internal email had been used for sending a promotional message without the agreement of either the trust or the recipients. Further the representative had created her own piece of promotional material for OxyNorm but had not had it certified prior to use in accordance with the Code. As a result the Panel noted that at the very least the email failed to meet the requirements of the Code regarding the provision of prescribing information.

The Panel considered that the representative had failed to maintain a high standard of ethical conduct; neither had she complied with all the relevant clauses of the Code. A breach of the Code was ruled. The Panel ruled a further breach of the Code as prior permission to send the email had not been obtained from those who received it.

COMPLAINT

The secretary to a hospital NHS foundation trust complained that a representative from Napp Pharmaceuticals Limited had persuaded a member of the trust administrative staff to let her make use of the trust's internal email system to promote OxyNorm (oxycodone) for injection to anaesthetists. The representative's request to the member of staff who gave her access to the email system was that she needed to send a message urgently to the consultant anaesthetist staff, and she then proceeded to send the message. A copy was provided.

The complainant stated that the use of such tactics to promote products was inappropriate and unacceptable. The complainant had written to the anaesthetist staff members to make it clear that the trust was not endorsing the company or its product. Such behaviour would not be tolerated in the future.

Napp was asked to respond in relation to the requirements of Clauses 9.9 and 15.2 of the Code.

RESPONSE

Napp submitted that the representative acted with the best of intentions, but not in the most appropriate way. The representative had an unblemished record since joining Napp and, it was believed, in her previous employment with another pharmaceutical company. She was eager to ensure that doctors were aware that an alternative to diamorphine, which was in short supply, was available, but on the spur of the moment she failed to stop and consider whether she was following the best approach. As soon as she knew she had caused offence, she apologised to the hospital pharmacist and acknowledged that it would have been preferable, in the first instance, if she had contacted the pharmacy with the information in question.

Napp submitted that there was no element of coercion on the part of the representative. She had met with this member of the trust's administrative staff on a number of occasions and had a good working relationship with her. On this visit, the representative openly said that she wanted to alert the anaesthetics team to the possibility of using OxyNorm injection instead of diamorphine, of which there was a shortage. She asked the administrator's advice on the best way of communicating this and it was the administrator who suggested using the trust's internal email system. The representative dictated the communication to the administrator and did not have direct access to the internal email system. In the circumstances, it did not occur to her that she needed any additional permission to make use of the email system in this way.

PANEL RULING

The Panel noted that the email sent by the representative referred to the diamorphine shortage and availability and use of OxyNorm injection as an alternative in moderate to severe post-operative pain. The representative had, in effect, written her own piece of promotional material.

The Panel considered that the representative's actions were totally unacceptable; there appeared to be a serious lack of understanding of the requirements of the Code. The trust's internal email had been used for sending a promotional message without the agreement of either the trust or the recipients. Further the representative had created her own piece of promotional material for OxyNorm but had not had it certified prior to use in accordance with Clause 14 of the Code. As a result the Panel noted that at the very least the email failed to meet the requirements of a number of subsections of Clause 4 of the Code.

The Panel considered that the representative had failed to maintain a high standard of ethical conduct; neither had she complied with all the relevant clauses of the Code. A breach of Clause 15.2 of the Code was ruled. The Panel also ruled a breach of Clause 9.9 as prior permission to send the email had not been obtained from those who received it.

Complaint received **13 January 2005**

Case completed **9 February 2005**

CASE AUTH/1676/1/05

GENERAL PRACTITIONER v PFIZER

Celebrex 'Dear Healthcare Professional' letter

In Case AUTH/1648/11/04, a general practitioner complained about a 'Dear Healthcare Professional' letter about Celebrex (celecoxib) issued by Pfizer. The general practitioner appealed the Panel's rulings of no breach of the Code in that case and at the same time alleged an additional breach of the Code. Following advice from the Authority, the general practitioner requested that his new allegation, which had not been the subject of a ruling by the Panel, be taken up with Pfizer as a fresh complaint (Case AUTH/1676/1/05).

The complainant alleged that the 'Dear Healthcare Professional' letter appeared not to comply with the requirement that promotional material must not include any reference to the Committee on Safety of Medicines (CSM) unless specifically required to do so by the licensing authority. If the reference to the CSM in the letter was not authorized by the CSM, the complainant saw no reason why the CSM was mentioned other than to suggest to the reader that the cardiovascular safety of celecoxib was endorsed by the CSM, over and above other COX-2 selective inhibitors. This was grossly misleading.

The Panel noted that the letter referred to a statement issued by the CSM. No evidence was submitted by Pfizer that the licensing authority had required a reference to the CSM. A breach of the Code was ruled as alleged and as acknowledged by Pfizer.

In Case AUTH/1648/11/04, a general practitioner complained about a 'Dear Healthcare Professional' letter (ref CEL 1249) about Celebrex (celecoxib) sent by Pfizer Limited. The general practitioner appealed the Panel's rulings of no breach of the Code in that case and at the same time alleged a breach of Clause 9.5 of the Code. The general practitioner was advised that a new allegation, which had not been the subject of a ruling by the Panel, could not be considered in the appeal. The matter could be taken up with Pfizer as a fresh complaint. The general practitioner stated that he wanted the matter to be taken up with Pfizer and it was taken up as Case AUTH/1676/1/05.

COMPLAINT

The complainant alleged that the 'Dear Healthcare Professional' letter appeared not to comply with Clause 9.5 of the Code which stated that promotional material must not include any reference to the Committee on Safety of Medicines (CSM) unless specifically required to do so by the licensing authority. If the reference to the CSM in the letter was not authorized by the CSM, the complainant saw no reason why the CSM was mentioned other than to suggest to the reader that the cardiovascular safety of celecoxib was endorsed by the CSM, over and above other COX-2 selective inhibitors. This was grossly misleading.

RESPONSE

Pfizer accepted a breach of Clause 9.5 and apologised for the error.

PANEL RULING

The Panel noted that the letter referred to a statement issued by the CSM. No evidence was submitted by Pfizer that the licensing authority had required a reference to the CSM. A breach of Clause 9.5 was ruled as alleged and as acknowledged by Pfizer.

Complaint received **20 January 2005**

Case completed **18 March 2005**

CODE OF PRACTICE REVIEW – MAY 2005

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1577/4/04	**General Practitioner v GlaxoSmithKline**	**Meeting on triptans**	**Breach Clause 9.1**	**No appeal**	**Page 3**
1609/7//04	**Merck Sharp & Dohme v Pfizer**	**Celebrex leavepiece**	**Six breaches Clause 7.2 Four breaches Clause 8.1 Public reprimand by ABPI Board**	**Appeal by respondent Report from Panel to Appeal Board Report to ABPI Board**	**Page 5**
1617/8/04	**General Practitioner/ Director v Wyeth**	**Alleged breach of undertaking and conduct of representatives**	**Breaches Clauses 7.2 and 15.2**	**No appeal**	**Page 19**
1626/8/04	**Primary Care Trust Pharmacist v GlaxoSmithKline**	**Implementation of a service**	**Breaches Clauses 7.2, 7.4 and 7.5**	**Appeal by complainant**	**Page 23**
1629/9/04	Head of Medicines Management/Director v Wyeth	Alleged breach of undertaking	No breach	No appeal	Page 36
1634/9/04	**Bristol-Myers Squibb and Otsuka v Lilly**	**Promotion of Zyprexa**	**Three breaches Clause 7.2 Two breaches Clause 7.8**	**Appeal by respondent**	**Page 39**
1635/9/04	**AstraZeneca v GlaxoSmithKline**	**Promotion of Seretide**	**Breach Clause 3.2 Eleven breaches Clause 7.2 Ten breaches Clause 7.4 Eight breaches Clause 7.10**	**No appeal**	**Page 47**
1641/10/04	**Roche v Novartis**	**Prescribing information for Myfortic**	**Breach Clause 4.1**	**Appeal by respondent**	**Page 58**
1645/10/04	**Pfizer Consumer Healthcare v GlaxoSmithKline Consumer Healthcare**	**NiQuitin CQ Clinical Guide**	**Breach Clause 4.9 Two breaches Clause 7.2 Two breaches Clause 7.8**	**No appeal**	**Page 63**
1646/10/04, 1647/10/04 and 1663/12/04	**Hospital Doctor, Pharmacist and Anonymous v GlaxoSmithKline**	**The Sunday Times Asthma supplement**	**1646/10/04 Breaches Clauses 10.1, 20.1 and 20.2 1647/10/04 and 1663/12/04 Breaches Clauses 20.1 and 20.2**	**No appeal**	**Page 70**
1649/10/04	Primary Care Trust Prescribing Adviser v Wyeth	Promotion of Prostap SR	No breach	No appeal	Page 76

1650/11/04	**Hospital Consultant v Wyeth**	**Conduct of representatives**	**Breaches Clauses 2, 9.1, 15.2, 19.1 and 20.1**	**No appeal**	**Page 80**
1651/11/04	Novo Nordisk/Director v Sanofi-Aventis	Alleged breach of undertaking	No breach	No appeal	Page 84
1653/11/04	Prescribing Adviser v Sankyo	Promotion of Olmetec	No breach	No appeal	Page 88
1654/11/04	**Health Board Prescribing Advisor v Pfizer**	**Cardura XL leavepiece**	**Five breaches Clause 7.2 Four breaches Clause 7.4**	**No appeal**	**Page 90**
1655/11/04	**Practice Pharmacist/ Director v Wyeth**	**Switch programme and an alleged breach of undertaking**	**Breach Clause 18.1**	**No appeal**	**Page 93**
1656/11/04	Pharmaceutical Advisor v Amdipharm	Computer memory stick as promotional aid	No breach	No appeal	Page 98
1657/11/04	General Practitioner/ Pharmaceutical Company Consultant v AstraZeneca	Invitation to a meeting	No breach	No appeal	Page 99
1658/11/04	**General Practitioner v Lundbeck**	**Arrangements for a meeting**	**Breaches Clauses 9.1 and 19.1**	**No appeal**	**Page 100**
1660/12/04	Aventis Pasteur MSD v GlaxoSmithKline	Offer of compensation for cancelled orders	No breach	No appeal	Page 102
1661/12/04	**General Practitioner v Pfizer**	**Conduct of representatives**	**Breach Clause 9.1**	**No appeal**	**Page 105**
1662/12/04	**Voluntary admission by Merck Sharp & Dohme**	**Breach of undertaking**	**Breach Clause 22**	**No appeal**	**Page 106**
1664/12/04	Company employee v Schering-Plough	ViraferonPeg patient information leaflet	No breach	No appeal	Page 108
1665/12/04	**General Practitioner v AstraZeneca**	**Announcement of a price reduction for Zoladex, Arimidex and Nexium**	**Breach Clause 4.3**	**No appeal**	**Page 111**
1666/12/04	Janssen-Cilag/Director v Napp	Promotion of Transtec	No breach	No appeal	Page 112
1668/12/04	Primary Care Trust Head of Medicines Management v Pfizer	Depo-Provera 'Dear Healthcare Professional' letter	No breach	No appeal	Page 116
1669/12/04 and 1670/12/04	General Practitioner v Lilly and Boehringer Ingelheim	Yentreve referral summary sheet	No breach	No appeal	Page 117
1675/1/05	**Hospital NHS Foundation Trust v Napp**	**Conduct of a representative**	**Breaches Clauses 9.9 and 15.2**	**No appeal**	**Page 119**
1676/1/05	**General Practitioner v Pfizer**	**Celebrex 'Dear Healthcare Professional' letter**	**Breach Clause 9.5**	**No appeal**	**Page 120**

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 such medicines made available to the general 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 or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- 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.

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 Nicholas Browne 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 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).