PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 24 MAY 1999

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.

Sanctions in reported cases

A recent article in the Consumer Policy Review, published by the Consumers' Association, referred to the fact that the sanctions applied are not set out alongside each case reported in the Code of Practice Review.

In each case where a breach is found, the company concerned has to give an undertaking to cease the use of the advertisement or practice in question, state when it ceased and give an assurance that it will take steps to avoid similar breaches of the Code in the future. That sanction applies to every case included in the Review in which a breach was ruled. It has not been considered necessary to state in every report where a breach of the Code was ruled that the requisite undertaking and assurance had been received. The back cover of the Review explains the position.

When additional sanctions are applied, such as a company being required to submit to an audit of its procedures for complying with the Code, or being reprimanded for its conduct by the ABPI Board of Management, then that fact is reported. Also specifically reported is any circumstance in which the Code of Practice Panel reports a company to the Code of Practice Appeal Board or where the Appeal Board reports a company to the ABPI Board. These circumstances could include, for example, a particularly serious breach of the Code, the failure of a company to give the requisite undertaking and assurance or failure to comply with an undertaking and assurance which a company has given.

Although often wrongly referred to by those outside the industry as 'fines', the administrative charges payable by pharmaceutical companies ruled in breach and pharmaceutical companies making unfounded complaints are not regarded as sanctions but as contributions to the running costs of the Authority, which is financially independent.

Samples supplied to the public

Clause 17.11 of the Code of Practice states that 'Unsolicited medicines must not be supplied to the general public' and the supplementary information to that clause states that 'Proposed amendments to the Advertising Regulations under consideration by the Medicines Control Agency at the time of going to press would prohibit the supply of medicines to the general public for promotional purposes, whether solicited or unsolicited.'

As advised in the February issue of the Review, new regulations have now been made, The Medicines (Advertising and Monitoring of Advertising) Amendment Regulations 1999 (SI 1999 No. 267) which came into force on 5 April. Copies are available from branches of HMSO, price £2.

The new regulations replace regulation 12 of The Medicines (Advertising) Regulations 1994 (SI 1994 No. 1932) with the following:

'No person –

(a) being the holder of a marketing authorization; or

(b) in the course of a business carried on by him and consisting (wholly or partly) of manufacturing relevant medicinal products or of selling or supplying relevant medicinal products,

shall for a promotional purpose (whether a promotional purpose of his own or of a third party) sell or supply any relevant medicinal product to any member of the public.'

When the Code is next revised it will be amended to reflect this change in the law.

Year 2000 edition of the Code of Practice

The current 1998 edition of the Code of Practice states that it is anticipated that the next edition will be published in the year 2000. A number of possible changes to the Code are under consideration of the present time but it is unlikely that these will be agreed during the current year so that a new edition could come into force on 1 January 2000.

It is still anticipated that there will be a year 2000 edition but it is expected that it will not come into operation until well on into that year.

Farewell to Vicki Meyrick...

Vicki Meyrick, who had been with the Authority since 1995 and was currently its Administrator and the Secretary to the Director, has left to take up a new post. The Authority thanks Vicki for all her hard work on its behalf and wishes her all the best for the future.

... welcome to Jean Rollingson

In Vicki's place the Authority has welcomed Jean Rollingson. Jean will from now on be responsible for organising the seminars on the Code of Practice which the Authority holds on a regular basis at the Royal Society of Medicine. Her telephone number is 0171-930 9677 extension 1443.

1998 Levy partially refunded

The Authority is financed principally by a levy payable by members of the ABPI and by administrative charges payable by pharmaceutical companies found in breach of the Code and pharmaceutical companies which make complaints which are not upheld. No charges are payable by complainants from outside the pharmaceutical industry.

The administrative charges resulting from the large number of complaints in 1998 (144 – as reported in the February Review) would have led to an undue surplus on the year and, to avoid that, ABPI member companies were refunded 60% of the levy which they had paid in 1998. Refunding levy in these circumstances means that the costs of the Authority are borne largely by those pharmaceutical companies which are actually involved in cases.

Following the refund, the surplus on the year for the Authority was £27,086 (before tax), its income being £493,953 and its expenditure £466,867. Administrative charges came to £330,000, the levy to £116,533 and income from meetings and seminars to £47,420.

CODE OF PRACTICE TRAINING

Training seminars on the Code of Practice, open to all comers, are run by the Code of Practice Authority on a regular basis at the Royal Society of Medicine in London.

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

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

Friday, 3 September

Wednesday, 13 October

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 (0171-930 9677 extn 1443).

How to contact the Authority

Our address is:

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

Telephone: 0171-930 9677
Facsimile: 0171-930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Jean Rollingson (0171-930 9677 extn 1443).

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

Heather Simmonds:	0171-747 1438
Etta Logan:	0171-747 1405
Jane Landles:	0171-747 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.

GENERAL PRACTITIONER v SCHERING-PLOUGH

Conduct of a representative

A general practitioner complained about comments made by a representative of Schering-Plough. It was alleged that the representative had made several disparaging references to Zirtek (cetirizine), a UCB Pharma product, saying that it was classified as a sedating antihistamine in the United States and would sedate up to 25% of people taking it, and that it interacted with alcohol and it was illegal in the United States to drive while taking it. Schering-Plough marketed Clarityn (loratadine).

The Panel noted that the entry for Zirtek in the ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998-99 stated that it had a low potential for drowsiness at pharmacologically active doses. Beneath the subheading 'Side effects' it stated that in objective tests of psychomotor function the incidence of sedation was similar to that of placebo. The Panel noted that the representative had stated that data was available to show that Zirtek was more sedating than placebo. The Panel noted that the data referred to by the representative included the US data sheet. The Panel considered that in the UK the UK data sheet or summary of product characteristics (SPC) took precedence and represented the agreed details about a product. The Panel considered that given the UK data sheet for Zirtek, the comments of the representative that cetirizine was more sedating than placebo were misleading and a breach of the Code was ruled.

Upon appeal by Schering-Plough, the Code of Practice Appeal Board noted that the parties' accounts of the conversation differed. The complainant stated that the representative had alleged that Zirtek was classified as a sedating antihistamine in the United States and would sedate up to 25% of the people taking it. The representative had stated that he had confirmed that data was available including review papers and the US data sheet showing that cetirizine was more sedating than placebo. The Appeal Board considered that there were important differences between the parties' accounts. It was difficult to know where the truth lay. The Appeal Board considered that it was not possible to determine precisely what had been said by the representative and therefore ruled no breach of the Code.

The Panel noted that the UK data sheet for Zirtek stated that 'As with other antihistamines it is advisable to avoid excessive alcohol consumption'. The Clarityn SPC stated, beneath the heading 'Interactions', that when administered concurrently with alcohol Clarityn had no potentiating effects as measured by psychomotor performance studies. The Panel considered that, on balance, the statement made by the representative that Zirtek interacted with alcohol was not unreasonable and ruled no breach of the Code.

The Panel noted the complainant's allegation that the representative had stated that it was illegal to drive whilst taking Zirtek in the USA. The representative denied making any claim in respect of driving and Zirtek in the United States or elsewhere. The parties' accounts differed. It was difficult to determine where the truth lay. In the absence of conclusive evidence the Panel ruled no breach of the Code in this regard.

A general practitioner complained about statements made by a representative from Schering-Plough Ltd about the antihistamine Zirtek (cetirizine) marketed by UCB Pharma Ltd. Schering-Plough marketed Clarityn (loratadine).

COMPLAINT

The complainant stated that he had attended a medical meeting and associated exhibition which had been held at a hotel. It was whilst he was viewing the exhibition that he had the opportunity to talk to one of the Schering-Plough representatives. At the start of the conversation the representative asked the complainant which antihistamine he tended to favour and the complainant stated that he used Zirtek. During the course of the conversation the Schering-Plough representative made several references to Zirtek which the complainant believed were of a disparaging nature and in breach of the Code. The statements made by the representative were that Zirtek was classified as a sedating antihistamine in the United States and would sedate up to 25% of people taking it. Zirtek interacted with alcohol and it was illegal to drive whilst taking Zirtek in the United States.

The complainant stated that one of his colleagues at work had confirmed that he had also had contact with one of the local Schering-Plough representatives in a face to face meeting in the surgery during which very similar claims were made regarding Zirtek.

RESPONSE

Schering-Plough confirmed that its representative met with the complainant three months before the date of the letter of complaint at the medical exhibition. The representative's account of their discussion was, however, in some areas, at variance with that from the complainant.

The representative stated that he confirmed that Clarityn was a non-sedating antihistamine. He also stated that data was available, including review papers and the US data sheet, showing that cetirizine was more sedating than placebo.

The representative stated that he pointed out that there was no data showing interaction of Clarityn with alcohol though there was data to show that, when taken together, alcohol and cetirizine were additive in their sedative effect.

The points and claims made by the representative were done so verbally, without reference to printed materials. The representative categorically denied making any claim in respect of driving and cetirizine in the United States or elsewhere.

Schering-Plough confirmed that the representative had passed the ABPI medical representatives' examination.

With reference to the complainant's point that similar claims were made to his partner in a face to face meeting in the surgery, Schering-Plough found this difficult to comment on. Its database of customer contacts, which it monitored closely, showed no Schering-Plough representative contact with the complainant's partners either in a face to face or other meeting in the last twelve months at the surgery.

Schering-Plough provided a copy of the representative's briefing document issued in March 1998, which covered the period of this meeting. It believed that its direct instructions on Clarityn product messages were clear and consistent with all aspects of the Code. In conclusion, Schering-Plough did not believe the claims made by its representative on 10 June with respect to cetirizine were in breach of Clause 7.2 of the Code.

* * * * *

Prior to making a ruling the response was passed to the complainant for comment.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that he stood by his original comments concerning his conversation with the representative. The complainant appreciated that it would be very difficult as it would appear to amount to the representative's word against his and he did not know how this difference of opinion could be resolved.

The complainant stated that he had discussed this with his colleague, who had confirmed that someone had spoken to him along very similar lines. The complainant noted that Schering-Plough's database of customer contacts did not show any meeting between his colleague and the company representative. This might be accounted for by the fact that his colleague was a fairly recent partner to the practice. The meeting might not have been entered as his colleague was not on the database at the time of the meeting or, indeed, his colleague might have been mistaken and the meeting did not occur at the surgery but occurred whilst he was a general practitioner based elsewhere.

PANEL RULING

The Panel noted that no printed material was referred to by the representative during his conversation with the complainant. The Panel examined the detail aid which covered the period of the meeting as this would give some indication of the messages being promoted. The detail aid which had been provided by the company for another purpose included the claim 'Sedating antihistamines are banned for drivers in 36 states of the USA – unlike some antihistamines, Clarityn is classed as non-sedating worldwide!' The Panel examined the relevant briefing material which stated that the aim of the relevant page of the detail aid was to raise the importance of sedation as an issue and to illustrate that Clarityn was truly non-sedating.

The Panel noted that the entry for Zirtek in the ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998-99 stated that it had a low potential for drowsiness at pharmacologically active doses. Beneath the subheading 'Side effects' it stated that in objective tests of psychomotor function the incidence of sedation was similar to that of placebo.

The Panel noted that the representative had stated that data was available to show that Zirtek was more sedating than placebo. The Panel noted that the data referred to by the representative included the US data sheet. The Panel considered that in the UK the UK data sheet or summary of product characteristics (SPC) took precedence and represented the agreed details about a product. The Panel considered that given the UK data sheet for Zirtek, the comments of the representative that cetirizine was more sedating than placebo were misleading and a breach of Clause 7.2 of the Code was ruled.

The Panel noted that the UK data sheet for Zirtek stated that 'As with other antihistamines it is advisable to avoid excessive alcohol consumption'. The Clarityn SPC stated, beneath the heading 'Interactions', that when administered concurrently with alcohol Clarityn had no potentiating effects as measured by psychomotor performance studies: The Panel considered that, on balance, the statement made by the representative that Zirtek interacted with alcohol was not unreasonable and ruled no breach of the Code.

The Panel noted the complainant's allegation that the representative had stated that it was illegal to drive whilst taking Zirtek in the USA. The representative denied making any claim in respect of driving and Zirtek in the United States or elsewhere. The detail aid and briefing material stated that 'Fatal accidents are more likely in drivers taking sedating antihistamines' and 'Sedating antihistamines are barred in 36 states in the USA.' The parties' accounts differed. It was difficult to determine where the truth lay. In the absence of conclusive evidence the Panel ruled no breach of the Code in this regard.

APPEAL BY SCHERING-PLOUGH

Whilst Schering-Plough accepted that cetirizine had, compared to the older, sedating antihistamines a lower potential for drowsiness, this did not conflict with the fact stated by its representative that cetirizine was more sedating than placebo. There was a wealth of data to support this statement.

The incidence of sedation with cetirizine might be considered low but it was significantly higher than that of placebo. Schering-Plough suggested that it was indeed, for that reason, that cetirizine's labelling – in contrast to other antihistamines such as loratadine – was required to include the fact of the potential for sedation.

Numerous studies had found that cetirizine was more sedating than placebo. The largest and most robust database that confirmed this fact was a meta-analysis of the pre-registration, placebo controlled trials using a maximum dose of 10mg of cetirizine that were submitted in the United States by cetirizine's sponsors in support of their application for marketing authorization. (The registered dose for Zirtek in the UK data sheet was one 10mg tablet daily). These data were referenced in the US Summary Basis of Approval for cetirizine.

In these studies 2,034 individuals were given 5mg or 10mg of Zirtek. A somnolence rate of 13.7% was recorded in these patients. The 1,612 patients in the placebo arm had a somnolence rate of 6.3%. The document further recorded that the 'incidence of somnolence associated with Zirtek was dose-related, 6% in placebo, 11% at 5mg and 14% at 10mg.' The findings of this large, validated series had been confirmed in many other published studies conducted in a number of countries between 1989 and 1997.

Schering-Plough conducted a search for placebo controlled studies involving cetirizine, searching for references from reviews of sedation and a database search of Medline and Excerpta Medica. All the studies Schering-Plough found which involved 20 or more patients were included and the results of these studies further confirmed the representative's claim that cetirizine had a higher incidence of sedation than placebo.

The three largest (and therefore probably most robust) studies by Falliers *et al* (1991), Lockey *et al* (1996) and Meltzer *et al* (1996), involving respectively: 419, 311 and 279 patients, all showed a statistically significantly higher incidence of somnolence, drowsiness or sedation with cetirizine compared to placebo.

Examining the 10 largest studies in this series of 22, 9 of the 10 (90%) had at least a numerically superior incidence of sedation with cetirizine than placebo.

Moving to the smaller, and possibly less robust studies, but those which still had greater than 100 patients enrolled, Schering-Plough found 12 out of 16 (75%) of the studies showed at least a numerically higher sedation rate for cetirizine than placebo.

Overall, of the 21 studies identified, 15 (71%) showed at least a numerically higher sedation rate with cetirizine than placebo.

Schering-Plough submitted that it might help place in context the significance of this search in demonstrating that cetirizine was more sedating than placebo to examine a similar search, using the same parameters, but comparing loratadine and placebo.

A summary table of such a search was provided. In 26 studies conducted between 1988 and 1998, with patient enrolment ranging from 24 to 338 subjects, there was not a single study able to demonstrate a statistically significant difference between loratadine and placebo.

The meta-analysis of all the US trials performed before cetirizine was licensed, and the extensive search of placebo randomised trials involving cetirizine, both came to the same conclusion; that cetirizine was more sedating than placebo.

Schering-Plough believed that this data demonstrated that the statement its representative made was based on an up to date evaluation of all the evidence and that it reflected that evidence clearly in accordance with Clause 7.2 of the Code of Practice.

Whilst perhaps not directly related to the claim, it was interesting to note that comparisons of studies comparing cetirizine with other antihistamines known to be non-sedating had shown results consistent with those in placebo controlled studies. For example, Backhouse *et al* (1990) compared terfenadine with cetirizine at the recommended therapeutic doses for one week. Drowsiness was reported in ten cetirizine compared with only two terfenadine treated patients.

With respect to a more objective assessment of sedative performance, Ramaekers *et al* (1992) demonstrated driving impairment in 16 healthy volunteers receiving cetirizine but none with loratadine.

Similarly, a search using the same parameters as the earlier searches but comparing cetirizine and loratadine also showed consistent results. Five studies were identified involving a total of 835 patients. In four of these studies cetirizine was found to cause more drowsiness than loratadine. A review article by Van Cauwenberge (1992) concluded after reviewing controlled studies involving a total of 616 patients that 'the CNS profile (specifically sedation) of loratadine was… better than that of cetirizine'. The data was summarised in a table provided to the Appeal Board.

As the incidence of sedation with both terfenadine and loratadine was equivalent to placebo it was possible to infer that cetirizine had greater sedating potential than placebo.

This was not disproved by the few psychomotor studies, generally sponsored by cetirizine's developers, which were also reflected in cetirizine's labelling. These studies were often too small (in terms of number of subjects, usually less than 20) to detect a sedation effect. They also were generally performed using healthy volunteers, rather than allergy patients, so that they could not measure the effect of the drug in the actual disease state it was used to treat. They did not counter the overwhelming weight of scientific evidence, as discussed above, that cetirizine did have a greater potential for sedation than placebo.

Schering-Plough stated that in at least two countries, the United States and Holland, the licence holders of cetirizine had been restrained in law, voluntarily and involuntarily, from making the claim that cetirizine was non-sedating. In the United States the company responsible for marketing cetirizine admitted in a 1996 settlement agreement with Schering Corp that it would not claim that cetirizine was non-sedating or essentially non-sedating, or that cetirizine was as non-sedating as Clarityn (loratadine). It further agreed that, as of that time, claims that cetirizine was non-sedating were 'not adequately supported by existing clinical data.' In Holland, the trial court ordered the company holding the licence for cetirizine to notify physicians in writing that its claim that cetirizine had 'no sedation in the recommended dosage' was 'misleading and unlawful'. This ruling was upheld on appeal. Whilst this agreement and restraining order clearly did not cover the UK, it might be considered at least suggestive evidence that cetirizine was not as non-sedating as placebo when both the licence holders of cetirizine themselves and the Dutch courts had agreed that the product could not be claimed to be non-sedating.

In summary, therefore, Schering-Plough believed it had been able to demonstrate that the statement by its representative that cetirizine was more sedating than placebo was an accurate reflection of the facts. In addition this statement was completely compatible with the UK labelling for cetirizine.

APPEAL BOARD RULING

The Appeal Board noted that the parties' accounts of the conversation differed. The complainant stated that the representative had alleged that Zirtek was classified as a sedating antihistamine in the United States and would sedate up to 25% of people taking it. The representative had stated that he had confirmed that data was available including review papers and the US data sheet showing cetirizine was more sedating than placebo. The Appeal Board considered that there were important differences between the parties' accounts. It was difficult to know where the truth lay. The Appeal Board considered that it was not possible to determine precisely what had been said by the representative and therefore ruled no breach of the Code.

The appeal was successful.

Complaint received **11 September 1998**

Case completed **28 January 1999**

CASE AUTH/780/10/98

GLAXO WELLCOME v MERCK SHARP & DOHME

Maxalt detail aid

Glaxo Wellcome complained about a detail aid for Maxalt (rizatriptan) issued by Merck Sharp & Dohme. Glaxo Wellcome marketed Imigran (sumatriptan).

The claim 'Faster headache relief than sumatriptan 100mg' appeared as a heading but Glaxo Wellcome did not consider that there was sufficient evidence to support it. On balance, Glaxo Wellcome believed that both rizatriptan and Imigran had a similar speed of onset. Two comparative trials had shown both treatments to be equally effective at 30 minutes. The Panel noted that in the study upon which the claim was based more patients reported pain relief at all time points (0.5, 1, 1.5 and 2 hours) in the rizatriptan 10mg group than in the sumatriptan 100mg group. The difference between the two groups was only statistically significant at 1 hour. The Panel considered that the unqualified claim was misleading and a breach of the Code was ruled.

The claim 'Faster absorption than sumatriptan 100mg' was alleged to be neither a fair nor a balanced evaluation of the available data. The significant difference in tmax values for rizatriptan and sumatriptan indicated in the detail aid was based on a comparison of sumatriptan 100mg and varying doses of rizatriptan, some of which were not licensed. A median tmax was obtained which included unlicensed doses. A literature search on sumatriptan studies showed a tmax value less than the study quoted in the detail aid. No mention was made of the increase in tmax for rizatriptan resulting from administration together with food. The Panel considered that, given the data and the information in the Maxalt summary of product characteristics (SPC), the bar chart was not misleading with regard to the tmax for either rizatriptan or sumatriptan. Nevertheless the Panel considered that given the statements in the Maxalt SPC about the effect of food or the fed state on absorption, the claim 'Faster absorption than sumatriptan 100mg' was misleading as it was not sufficiently qualified and a breach of the Code was ruled.

The claim 'More effective elimination of associated symptoms than sumatriptan 100mg' appeared as a heading. Glaxo Wellcome did not dispute that in the study cited rizatriptan provided more effective relief of nausea (from 30 minutes to 2 hours) and more effective relief of photo and phonophobia at 1 hour and 1.5 hours (but not at 30 minutes or 2 hours). This did not, however, reflect all the available data. In a study of rizatriptan 10mg against Imigran 50mg, rizatriptan was only significantly more effective than Imigran 50mg at relieving nausea at 1 and 1.5 hours. Both treatments were equally as effective at relieving photo and phonophobia at all time points studied, and by 2 hours Imigran 50mg was equally as effective as rizatriptan at relieving nausea. The Panel noted that the study referred to by Glaxo Wellcome was not powered specifically to compare relief of nausea, photophobia and phonophobia between rizatriptan 10mg and sumatriptan 50mg. The Panel considered that the claim, and the page in question, clearly related to a comparison of Maxalt 10mg with sumatriptan 100mg. The claim and the page accurately reflected the data. The Panel did not consider that the claim or the page were misleading and no breach of the Code was ruled.

Glaxo Wellcome UK Limited complained about a detail aid for Maxalt (rizatriptan)(ref 07-99 MXT.98.GB.(W6047)45038.DA.1mCW.798) issued by Merck Sharp & Dohme Limited, alleging that it contained misleading claims in breach of Clause 7.2 of the Code. Glaxo Wellcome marketed Imigran (sumatriptan).

1 Claim 'Faster headache relief than sumatriptan 100mg'

This claim appeared as a heading to page 5 of the detail aid and was followed by the claim 'Maxalt 10mg tablets provided faster headache relief within two hours than sumatriptan 100mg ($p<0.05$)'.

COMPLAINT

Glaxo Wellcome stated that it was currently in the process of complaining about a mailing sent out by Merck Sharp & Dohme to pharmacists prior to the launch of rizatriptan [Case AUTH/759/8/98]. One of the claims that it disputed was that rizatriptan provided faster relief of headache than Imigran. The claim was repeated in the detail aid.

Glaxo Wellcome did not believe that Merck Sharp & Dohme had sufficient evidence to be able to claim a faster onset of headache relief than Imigran 100mg.

Whilst it did not dispute that in one trial, rizatriptan 10mg against Imigran 100mg, rizatriptan was significantly more effective than Imigran at 60 minutes, there was no significant difference between the two treatments at 30 minutes.

In addition, a further trial of rizatriptan 10mg against Imigran 50mg found no significant difference in headache relief between the two treatments at either 30 minutes or 60 minutes.

The Imigran data sheet and the summary of product characteristics (SPC) for rizatriptan both stated that relief began around 30 minutes after dosing, indicating that both treatments had a similar onset of relief.

Thus, on balance, Glaxo Wellcome believed that both rizatriptan and Imigran had a similar speed of onset. Two comparative trials had shown both treatments to be equally as effective at 30 minutes.

RESPONSE

Merck Sharp & Dohme said that the statement was already the subject of a complaint (Case AUTH/759/8/98) but the wording was not identical.

Time to relief analysis
The claim was based on the primary end-point of the rizatriptan vs sumatriptan comparison study which showed a statistically significant difference ($p<0.05$) in terms of the age adjusted time to headache relief analysis. This type of analysis was commonly used in the analysis of clinical trials, and was also known as survival analysis or life table analysis. The concept and methods of such analyses were discussed in medical statistical textbooks (eg Dr D G Altman, Practical Studies for Medical Research) and were currently the subject of an ongoing series in the British Medical Journal. The concept (although different methods) had been utilised by Glaxo Wellcome in some migraine studies with sumatriptan. In the 030 study the analysis compared the time that patients first reported headache relief at time points up to 2 hours for rizatriptan 10mg vs sumatriptan 100mg.

The method used for the analysis, a variation of Cox regression, produced a summary statistic, the hazard ratio, which qualified the treatment comparison. The hazard ratio for rizatriptan vs sumatriptan 100mg was 1.21 ($p=0.032$). This meant that for any patient with a headache at a particular time point they were approximately 20% more likely to get relief of their headache within the next unit of time (second, minute, or whatever) with rizatriptan than with sumatriptan 100mg.

Therefore the claim was substantiated by the time to relief analysis, and quite deliberately no claim was made within the statement with regard to specific individual time points. (The difference in rates of headache relief at 1 hour was in fact statistically significant ($p=0.01$)). Whilst differences between rizatriptan 10mg and sumatriptan 100mg in the 030 study were not statistically significant at all the individual time points, rizatriptan provided numerically superior pain relief at all time points up to and including 2 hours. The results of this study were to be published in a peer-reviewed journal in the very near future. The validity of the use of the time to relief analysis in this context had now been confirmed by peer-review.

Comparison to sumatriptan 50mg
The comparison made in the claim was clearly with sumatriptan 100mg. Merck Sharp & Dohme had chosen this dose because it was well established as the gold standard of treatment; it was the most widely prescribed dose in the UK and was the market leader in terms of cash sales (IMS data for September 1998 showed cash sales of £2.2m and £1.0m for sumatriptan 100mg and 50mg respectively). It was therefore the most logical comparison and Merck Sharp and Dohme could not understand why Glaxo Wellcome continued to raise comparisons with the 50mg dose. Glaxo Wellcome again tried to muddy the waters by referring to specific time points with reference to the 046 study comparing rizatriptan with sumatriptan 50mg. In this study, rizatriptan was statistically significantly superior to sumatriptan 50mg in a time to relief analysis ($p=0.046$, hazard ratio 1.14). Again, at all time points within 2 hours rizatriptan was numerically superior to sumatriptan 50mg.

Merck Sharp & Dohme noted that Glaxo Wellcome came to the conclusion that 'Two comparative clinical trials have shown both treatments to be equally as effective at 30 minutes'. Merck Sharp & Dohme assumed that this mistake was based on the fact that the superiority of rizatriptan 10mg over sumatriptan 100mg and 50mg at the 30 minute time point did not reach the usual threshold for statistical significance of $p<0.05$. The number of patients required for the study was determined by the power for the time to headache relief analysis, not that to definitively establish superiority at 30 minutes. Because rizatriptan 10mg was numerically superior to sumatriptan at all time points for headache relief in two separate studies it was clear that the lack of statistical significance at this time point was a so called 'type II error' ie there was a real clinical difference between the treatments but there were insufficient patients to make the result statistically significant. It was the time to headache relief analysis which supported the claim, as discussed above and in Merck Sharp & Dohme's previous communications.

PANEL RULING

The Panel noted that in Case AUTH/759/8/98 it had considered the claim '…Maxalt 10mg tablets provide faster headache relief within 2 hours than sumatriptan 100mg' to be misleading in breach of Clause 7.2 of the Code. At some time points, ie 0.5, 1.5 and 2 hours, there had been no significant difference between treatments. The ruling had been accepted by Merck Sharp and Dohme. The claim now at issue, 'Faster headache relief than sumatriptan 100mg' was different although, like the previous claim, it was based on the results of study 030.

The Panel noted that in study 030, at all time points (0.5, 1, 1.5 and 2 hours), more patients reported pain relief in the rizatriptan 10mg group than in the sumatriptan 100mg group. The difference between the two groups was statistically significant at 1 hour.

A bar chart beneath the claim in question showed that at 1 hour 37% of patients reported headache relief on Maxalt 10mg compared with 28% in the sumatriptan group (p=0.01).

The Panel noted that the rizatriptan SPC stated that headache relief occurred as early as 30 minutes after dosing. The Imigran Tablets data sheet stated 'Clinical response begins around 30 minutes following oral administration'. The Panel did not consider that 'headache relief' and 'Clinical response begins' were synonymous. The first term related to outcome whereas the second related to onset of action. Although study 030 showed that some patients in both groups reported pain relief after 30 minutes, significantly more reported pain relief after 1 hour in the rizatriptan group than in the sumatriptan group.

The Panel considered that the unqualified claim 'Faster headache relief than sumatriptan 100mg' was misleading as there was only a statistically significant difference between the products at 1 hour. A breach of Clause 7.2 was ruled.

2 Claim 'Faster absorption than sumatriptan 100mg'

This claim appeared as a heading to page 4 of the detail aid. Beneath the claim was a bar chart which depicted time to maximum concentration (median tmax) for rizatriptan tablets (1.3 hours) and sumatriptan 100mg tablets (2.5 hours). The data was referenced to a study by Sciberras *et al* (1997).

COMPLAINT

Glaxo Wellcome stated that it had recently been in correspondence with Merck Sharp & Dohme regarding the above claim (copies of the correspondence were provided). Glaxo Wellcome considered the claim was neither a fair nor a balanced evaluation of all the available data in breach of Clause 7.2 of the Code.

The points of issue were as follows:

a) The significant difference in tmax values for rizatriptan and sumatriptan indicated in the detail aid was based on a comparison of sumatriptan 100mg and varying doses of rizatriptan (5mg to 60mg), many of which were unlicensed.

The claim, and graph supporting the claim, were referenced to a small (n=16) pharmacokinetic study of rizatriptan in varying doses (from 0.5mg to 80mg) against placebo in healthy subjects. At the end of this study, the subjects were all given Imigran 100mg.

The value of 1.3 hours obtained for rizatriptan was a median tmax obtained from all the dose levels studied (5-80mg) which obviously included unlicensed doses.

Rizatriptan, like Imigran, displayed multiple peaks and its rate of absorption was not proportional to the dose administered: the resulting tmax tended to increase with the dose administered. Hence, Glaxo Wellcome did not believe that the tmax value for rizatriptan should be averaged across doses.

A fairer comparison would be to compare the licensed dose of rizatriptan with the licensed dose of Imigran.

Although the tmax value for rizatriptan 10mg from this study was stated to be 1 hour this was based only on 6 patients.

b) The tmax value for Imigran did not reflect all of the available data.

The study used in support of this claim was not a true direct comparison of the pharmacokinetics of Imigran and rizatriptan at the licensed doses. In fact, ten of the sixteen patients given Imigran did not receive the recommended dose of rizatriptan (10mg).

As it was not a true comparison, Glaxo Wellcome believed that a fair comparison of the relative absorption profiles of these two triptans should reflect all of the available data.

c) Comparison of all available data

Glaxo Wellcome provided the tmax values (all in healthy volunteers) from literature searches on the pharmacokinetics of rizatriptan and sumatriptan.

Glaxo Wellcome stated that all of the studies for sumatriptan showed a value less than the 2.5 hours seen in the study quoted in the detail aid and the vast majority of the studies indicated a tmax value of between 1 and 1.5 hours which was similar to the range seen for rizatriptan.

d) Absorption of rizatriptan was delayed by food

Finally, as stated in the SPC for rizatriptan, the absorption of rizatriptan was delayed by approximately one hour when administered together with food. In a pharmacokinetic study of the effect of food on rizatriptan 40mg, the tmax value increased from 1.6 hours in fasted subjects to 2.9 hours in fed subjects. The pharmacokinetic variables for Imigran did not appear to be affected by food. As many migraine patients experienced food cravings prior to a migraine attack, rizatriptan would often be taken after food with a consequent delay in absorption. However, there was no mention made of this in the detail aid.

In summary, Glaxo Wellcome believed the claim that rizatriptan had a faster absorption than Imigran, based on a single indirect comparison of rizatriptan in varying doses against Imigran, was not a true reflection of all the available data and therefore in breach of Clause 7.2 of the Code.

RESPONSE

Merck Sharp & Dohme said that it was absolutely clear that the detail aid referred to rizatriptan tablets and deliberately did not use the word Maxalt, which would imply a rizatriptan dose of 5 or 10 mg. The data was clearly referenced to the Sciberras study and appropriate details of the study were provided below the relevant information in the detail aid. The company responded to the various points raised by Glaxo Wellcome as follows:

a) 'The significant difference in tmax values for rizatriptan and sumatriptan indicated in the detail aid was based on a comparison of sumatriptan 100mg and varying doses of rizatriptan (5mg-60mg), many of which were unlicensed.'

With regard to tmax across varying doses, Merck Sharp & Dohme stated that the evidence from two

studies presented confirmed that for rizatriptan tmax was independent of dose, therefore the use of data from varying doses was a valid one.

The information for the graph in the detail aid that compared tmax values between several rizatriptan doses and sumatriptan 100mg was taken from a paper published by Sciberass *et al*. In the section described as pharmacokinetic data it stated that 'values for tmax were tested across dose levels' (5-60mg) 'and the differences [between the tmax for the various doses of rizatriptan] were found to be not significant'.

It could be observed that when the dose was doubled from 5 to 10mg the tmax value slightly reduced and when the dose was doubled from 10 to 20mg the tmax value remained the same. On further doubling of the dose to 40 mg tmax increased modestly. But it was clear that tmax initially decreased, then remained the same before modestly increasing which did not support the claim by Glaxo Wellcome that 'the resulting tmax tends to increase with the dose administered'.

Results from a subsequent study confirmed that for tmax values, no relationship to dose was evident across the 2.5 mg to 15mg dose range of rizatriptan. Merck Sharp & Dohme believed that the above data provided evidence to support the use of a tmax value averaged across doses by demonstrating that, for the above doses of rizatriptan, the value of tmax was not statistically different between the doses.

In addition, it was well known that for sumatriptan the plasma profile after oral dosing demonstrated multiple peaking. Therefore although the comparison of sumatriptan 100mg with several doses of rizatriptan was not the most ideal comparison, in the light of no other direct comparison it was the best possible option. Certainly to compare tmax values from different studies would be inappropriate.

Finally, to address two further points raised by Glaxo Wellcome in relation to the Sciberras study, Merck Sharp & Dohme said that it would like to clarify that the use of the median tmax value was a regulatory request and was an appropriate statistic for the nature of the data. Secondly, that the very nature of a first administration study meant that several dose levels were used, including unlicensed doses, and in terms of subject numbers the use of six subjects was customary.

b) 'The tmax value for Imigran did not reflect all the available data'

c) 'Comparison of all the available data'

Merck Sharp & Dohme considered that the detail aid had reflected all the relevant data available for sumatriptan tmax values and that the additional information provided by Glaxo Wellcome was misleading and irrelevant.

Merck Sharp & Dohme stated that the additional published tmax values for sumatriptan supplied by Glaxo Wellcome (which it had been suggested more accurately reflected all the available data) needed to be viewed in the context of the dose formulation. Certain studies were based on unlicensed formulations of sumatriptan. Different formulations did not automatically produce similar plasma profiles and it was therefore only meaningful to examine the plasma profile data from the oral tablet formulation. Some of the results did not relate to the oral tablet formulation and were therefore of no value in the context of this complaint. In addition, it would be noted that information had not been included as to whether subjects were in the fed or fasted state prior to dosing.

Merck Sharp & Dohme pointed out that in a study not quoted by Glaxo Wellcome there were five arms. Results from two arms for the 200mg dose had been omitted which provided tmax values of 2.0 and 2.5 hours. Merck Sharp & Dohme added these results to those provided for completeness.

Merck Sharp & Dohme stated that it was made very clear in the detail aid that the 1.3 hours quoted for rizatriptan tablets referred to a median value for tmax obtained from the results of a study using single rising doses of 0.5 to 80mg. It had already been highlighted in a previous communication that the results for 10mg were more favourable towards rizatriptan than the overall results (tmax 1 hour vs 1.3 hours), but in the interest of a fair and balanced evaluation, the pooled data and analysis (as it appeared in the detail aid) had been used. The evidence had also already been presented that confirmed that tmax values for rizatriptan were independent of dose and therefore the use of a tmax value from varying doses of rizatriptan was appropriate.

Merck Sharp & Dohme stated that it was also apparent that the tmax values provided in the detail aid reflected the information in the SPC for rizatriptan 10mg and the US product information for sumatriptan 100mg, giving tmax values of 1.0 to 1.5 hours and 2.0 to 2.5 hours respectively. Merck Sharp & Dohme noted that no tmax information was included in the data sheet for sumatriptan tablets, making direct UK comparison impossible.

In summary Merck Sharp & Dohme concluded that the detail aid was a true reflection of the available data, and specifically the only head to head study.

d) Merck Sharp & Dohme considered that the complaint put forward by Glaxo Wellcome regarding the fact that absorption of rizatriptan was delayed by food was irrelevant.

The statement made by Glaxo Wellcome concerning food cravings was not substantiated by references and Merck Sharp & Dohme was not aware of any published data that would support it. The company noted that it was thought that where cravings occurred this was generally during the 24-36 hour period before a migraine began. It was therefore not necessarily the case that patients would have ingested significant amounts of food within a few hours prior to dosing. Secondly, approximately two-thirds of patients might have nausea prior to the need for treatment of their migraine and it was therefore unlikely that they would have taken food during the period immediately before the onset of the migraine.

Merck Sharp & Dohme pointed out that in the pharmacokinetic study of the effect of food on

rizatriptan 40mg the conditions were extreme in terms of food fat content and probably did not reflect normal day-to-day situations. In addition, it noted that 40mg was not the UK licensed dose.

In addition Merck Sharp & Dohme considered that the statement made by Glaxo Wellcome, 'the pharmacokinetic variables for Imigran do not appear to be affected by food', was potentially misleading. The US product information for sumatriptan tablets stated that 'tmax was delayed by 30 minutes after food'. Again there was no relevant information in the data sheet for sumatriptan tablets.

Merck Sharp & Dohme noted that no claim had been made in the detail aid that the absorption of rizatriptan was not affected by food and the company had not made any comparison to sumatriptan in relation to this point. It should also be noted that prescribers were directed to review the SPC before prescribing.

The detail aid was designed to enable the representative to provide the most important information to prescribers. Merck Sharp & Dohme did not think that the effect of food on the absorption of rizatriptan was as clinically important or relevant as gastric stasis ie delayed emptying of the stomach, associated with the presence of a migraine. The effect of gastric stasis would be to delay the absorption of some drugs. However, the absorption of rizatriptan would not be affected by this phenomenon.

In summary Merck Sharp & Dohme considered that the information in the detail aid was a true reflection of all the relevant data.

PANEL RULING

The Panel noted that the SPC for Maxalt stated that for tablets the mean peak plasma concentrations (cmax) were reached in approximately 1-1.5 hours (tmax). The median figure quoted in the detail aid was 1.3 hours.

The Panel noted that the study to which the data was referenced (Sciberras) had evaluated the pharmacokinetics of oral rizatriptan (0.5 – 80mg) in comparison with oral sumatriptan (100mg) in 16 fasted healthy volunteers. The normal dose of oral rizatriptan was 10mg for which a tmax of 1 hour was recorded. Results showed that the time to tmax increased with doses beyond 20mg and at 60mg tmax was 2.1 hours. The use of higher doses had thus skewed the results such that the median tmax shown (1.3 hrs) was higher than might have been observed if only a 10mg dose had been investigated (1 hour). The figure of 1.3 hours was within the range of 1-1.5 hours given in the SPC. The Panel also noted that the subject of the whole detail aid was Maxalt 10mg and considered that it would have been helpful if the bar chart in question had been clearer with regard to the doses of rizatriptan to which it referred.

The Panel noted that the SPC for Maxalt stated in Section 4.5 that the absorption of rizatriptan was delayed by approximately 1 hour when administered together with food and that therefore the onset of effect might be delayed when administered in the fed state. Section 5.2 of the SPC, pharmacokinetic properties, stated that administration of a high-fat breakfast would delay absorption for approximately 1 hour but would not affect the extent of absorption. The Panel noted the submission from Merck Sharp & Dohme that the US product information for sumatriptan tablets stated that tmax was delayed by 30 minutes after food although this information was not in the Imigran UK data sheet.

The bar chart depicted a median tmax of 2.5 hours for sumatriptan as reported by Sciberras *et al*. Glaxo Wellcome had submitted that the vast majority of studies indicated a tmax value of between 1 and 1.5 hours for sumatriptan. The Panel noted, however, that most of these studies had used oral solutions or a dispersible tablet, one study did not state the formulation, another study had used only a 25mg tablet and the remaining study which had investigated the pharmacokinetics of a 100mg tablet reported a tmax of 2 hours. The Panel noted Merck Sharp & Dohme's submission that the US product information gave tmax as 2-2.5 hours. There was however no tmax information in the Imigran Tablets data sheet.

The Panel considered that, given the data and the information in the Maxalt SPC, the bar chart was not misleading with regard to the tmax for either rizatriptan or sumatriptan. Nevertheless the Panel considered that given the statements in the Maxalt SPC about the effect of food or the fed state on absorption the claim 'Faster absorption than sumatriptan 100mg' was misleading as it was not sufficiently qualified. A breach of Clause 7.2 was ruled.

3 Claim 'More effective elimination of associated symptoms than sumatriptan 100mg'

This claim appeared as a heading to page 7 of the detail aid. The page featured a bar chart depicting the percentage of patients whose nausea was eliminated at 30 minutes with Maxalt 10mg (25%), sumatriptan 100mg (14%) and placebo (12%). A claim was also made below the bar chart regarding the elimination of photophobia and phonophobia at 1 hour.

COMPLAINT

Glaxo Wellcome did not dispute that in the study cited rizatriptan provided more effective relief of nausea (from 30 minutes to 2 hours), and more effective relief of photo and phonophobia (the other two major associated symptoms) at 1 hour and 1.5 hours (but not at 30 minutes or 2 hours).

However, this did not reflect all of the available data. In a study of rizatriptan 10mg against Imigran 50mg, rizatriptan was only significantly more effective than Imigran 50mg at relieving nausea at 1 and 1.5 hours. Both treatments were equally as effective at relieving photo and phonophobia at all time points studied, and by 2 hours Imigran 50mg was equally as effective as rizatriptan at relieving nausea.

Glaxo Wellcome believed that Merck Sharp & Dohme were being selective in only citing data against Imigran 100mg and therefore in breach of Clause 7.2 of the Code.

RESPONSE

Merck Sharp & Dohme stated that the comparison made in the detail aid was clearly with sumatriptan 100mg. However, once again Glaxo Wellcome attempted to draw inappropriate conclusions from studies with sumatriptan 50mg.

Glaxo Wellcome's interpretation of the data from the rizatriptan 10mg versus sumatriptan 50mg study was once again inaccurate. This study was powered to test two primary hypotheses, namely the comparison between rizatriptan 10mg versus sumatriptan 50mg with regard to time to pain relief, and the comparison between rizatriptan 5mg and 10mg versus placebo with regard to pain relief at 2 hours. Therefore this study was not powered specifically to compare relief of nausea, photophobia and phonophobia between treatments. To make the assumption that treatments were equally effective because the usual threshold of statistical significance had not been reached in this situation was again inappropriate.

However, one of the objectives of the study on which the information in the detail was based was to examine the effects of rizatriptan 10mg and sumatriptan 100mg on functional disability and associated symptoms and it would therefore seem more meaningful and relevant to use this data.

PANEL RULING

The Panel noted that the study referred to by Glaxo Welcome was not powered specifically to compare relief of nausea, photophobia and phonophobia between rizatriptan 10mg and sumatriptan 50mg. The Panel considered that the claim, and the page in question, clearly related to a comparison of Maxalt 10mg with sumatriptan 100mg. The Panel considered that the claim and the page accurately reflected the data and noted that Glaxo Wellcome did not dispute the results of the study. The Panel did not consider that the claim or the page were misleading and no breach of Clause 7.2 was ruled.

Complaint received **23 October 1998**

Case completed **9 February 1999**

CASES AUTH/785/10/98 and AUTH/794/11/98

GENERAL PRACTITIONER v BRISTOL-MYERS SQUIBB and SANOFI WINTHROP

Newspaper article about Plavix

A general practitioner complained about an article which had appeared in The Times which referred to Plavix (clopidogrel) as being a new medicine launched by Bristol-Myers Squibb. The article was headed 'Tablet a day to ward off strokes' and stated that Plavix was more expensive than aspirin but that its improved antiplatelet activity and relative freedom from side effects made it a useful addition to the armoury employed in the treatment of vascular disease. The article referred to the CAPRIE study, a trial of clopidogrel versus aspirin in patients at risk of ischaemic events. The complainant said that in his opinion the article was encouraging patients to come to their doctor to request Plavix instead of aspirin. In patients with strokes there was absolutely no evidence, according to the CAPRIE study, of a reduced recurrence of events. The effect of the article was to waste doctors' time. The complainant had had several patients come in whose expectations had been falsely raised.

The complaint was taken up with both Bristol-Myers Squibb and Sanofi Winthrop as there was an agreement between them for the co-development and marketing of Plavix.

There was no claim in the press information pack that Plavix prevented strokes. It referred to the combined end point of myocardial infarction, ischaemic stroke and vascular death and was not misleading in that regard. The news release in the pack stated that 'Plavix prevents an estimated 26% more events than aspirin'. The calculation was based on the results of the CAPRIE study of a relative risk reduction of 8.7% in favour of Plavix. If the data from the Antiplatelet Trialists' Collaboration, which showed that aspirin prevented 25% of vascular events compared to no treatment/placebo, was extrapolated to the CAPRIE population, this would represent an additional 26% reduction in the number of events prevented with Plavix versus aspirin.

The Panel noted that the newspaper article stated, when referring to the CAPRIE study, that 'It showed that Plavix prevented an estimated 26 per cent of instances of serious trouble in people who had already had a history of strokes'. The press materials stated in bold the claim 'This represents an additional 26% reduction in the number of events prevented with Plavix versus aspirin'. The Panel considered that given the prominence attached to these claims, the press materials could have been clearer with regard to the calculation of the figure of 26% which was calculated using an extrapolation from a meta analysis and related to vascular events, not simply stroke.

The Panel did not consider that the press information constituted an advertisement for a prescription only medicine to the general public as alleged. On balance the press information pack was not unreasonable in relation to the requirements of the Code and no breach of the Code was ruled.

Upon appeal by the complainant, the Appeal Board considered that the article was inaccurate. It referred to a tablet a day to ward off strokes when the indication for Plavix was for the reduction of atherosclerotic events. Further, the article referred to

Plavix preventing an estimated 26% of instances of serious trouble in people who had a history of strokes and advanced coronary artery disease.

The Appeal Board was concerned about the basis for the claim in the press information pack that Plavix prevented an additional 26% in the number of events compared to aspirin. The extrapolation of results from the Antiplatelet Trialists' Collaboration data to the CAPRIE study assumed that the two patient populations were comparable. The Appeal Board considered that it was not appropriate at this stage to assume that this was so. The Appeal Board noted caveats in the SPC regarding the CAPRIE data. The Appeal Board considered that the press information pack was misleading and ruled breaches of the Code.

A general practitioner complained about an article which had appeared in The Times on 22 October 1998 and which referred to Plavix (clopidogrel) as being a new medicine launched by Bristol-Myers Squibb. It stated, *inter alia*, that it was more expensive than aspirin but that its improved antiplatelet action and relative freedom from side effects made it a useful addition to the armoury employed in the treatment of vascular disease. The article was headed 'Tablet a day to ward off strokes' and referred to data from a study. The study in question was a trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE).

A joint response was received from Bristol-Myers Squibb Pharmaceuticals Limited and Sanofi Winthrop Limited as there was an agreement between the two companies for the co-development and marketing of Plavix.

COMPLAINT

The complainant stated that in his opinion the article was encouraging patients to come to their doctor requesting Plavix instead of aspirin.

In patients with strokes there was absolutely no evidence, according to the CAPRIE study, of a reduced recurrence of events when comparing aspirin with Plavix, and, therefore, there was no justification for suggesting that patients should come and see their doctor to try this new medicine at a cost of almost £500 per annum, although this was the undoubted intention of the article. The headline indeed was a 'Tablet a day to ward off strokes'. The effect of the article was to waste doctors' time. The complainant had had several patients coming in to whom he had to explain the results of the CAPRIE study, which had a) falsely raised the expectations of the patients and b) wasted valuable doctors' time. At a time when doctors were struggling to stay within their prescribing budgets it was particularly irresponsible for Bristol-Myers Squibb to allow such an article to appear in a national newspaper, especially The Times which was read by literate patients who were likely to consult their general practitioner and this, the complainant suspected, was a deliberate ploy for increasing sales which had obviously been slow to take off some months after launch.

RESPONSE

Bristol-Myers Squibb and Sanofi Winthrop were sorry to hear that the article had created unnecessary work and possible embarrassment for the complainant. The article was not solicited by either Sanofi Winthrop or Bristol-Myers Squibb and they had no knowledge of its proposed content or even its existence, prior to publication. It was certainly not their intention to raise public expectations via articles in the mainstream press and for this reason the companies had restricted the focus of their press releases to the medical and scientific press only. Press packs had, however, been made available to some of the quality broadsheets for information only.

A copy of the press pack was provided. It was a comprehensive folder that dealt, in a fair and balanced fashion, with all aspects of cardiovascular, cerebrovascular and peripheral vascular disease. The 'background sheets' provided a comprehensive overview of the pathogenesis and epidemiology of atherosclerotic disease, together with the evidence and rationale for a 'multiple-risk-factor-intervention' approach. As part of this multiple risk factor approach, lifestyle changes (eg, weight loss, exercise, cessation of smoking) were strongly advocated and the information regarding pharmacological intervention discussed all accepted forms of medical therapy currently used for both primary and secondary prevention of atherosclerotic events. The section dealing with antiplatelet therapy (Backgrounder 3) discussed, in addition to clopidogrel, both of the other forms of antiplatelet therapy (ie aspirin and dipyridamole) that were currently licensed (ie licensed at the time that clopidogrel was launched) for treatment of atherosclerotic disease in the UK.

Two of the supplementary sheets, the 'fact sheet' and 'Backgrounder 1', dealt specifically with clopidogrel (Plavix). The former covered the licensed indications, mechanism of action, a brief description of the CAPRIE study and cost, while the latter described the rationale, methodology, results and conclusions of the CAPRIE trial in more detail.

CAPRIE was published in The Lancet. It was a multi-centre, randomized controlled trial, involving more than 19,000 patients, in which clopidogrel was compared to medium dose aspirin for prevention of the combined endpoint 'myocardial infarction, ischaemic stroke or vascular death' in patients with recent myocardial infarction (from a few days until less than 35 days), recent ischaemic stroke (from 7 days until less than 6 months), or established atherosclerotic peripheral vascular disease. CAPRIE clearly demonstrated the effectiveness and safety of clopidogrel compared to medium dose aspirin, and it was the pivotal study upon which worldwide licensing had been granted. As was concluded in The Lancet, '…in a patient population similar to that in CAPRIE, aspirin would be expected to prevent about 19 major clinical events versus 24 with clopidogrel, for each 1000 patients treated for one year' and 'clopidogrel is at least as safe as medium dose aspirin…'. In the trial summary the CAPRIE Steering Committee concluded that 'Long-term administration of clopidogrel to patients with atherosclerotic vascular

disease is more effective than aspirin in reducing the combined risk of ischaemic stroke, myocardial infarction or vascular death.' These conclusions were fully substantiated by the results of CAPRIE and no additional claims were made in the press pack.

The essence of the complaint about the article seemed to be that the heading 'Tablet a day to ward off strokes' implied that clopidogrel was independently effective at preventing strokes. This claim was not made in the press pack. The press pack quite clearly pointed out that, in accordance with the licence, the end point used in CAPRIE was the combined endpoint, 'myocardial infarction, ischaemic stroke and vascular death.'

Independent journalists were, of course, at liberty to write and publish articles as they saw fit and the companies had no jurisdiction over the content of such articles, or the headlines that they chose to use. Under these circumstances, it was the responsibility of the paper and the journalist to ensure that such articles were factually correct and not misleading.

In summary, the press pack represented a balanced, objective and up to date presentation of the evidence concerning both clopidogrel and the other treatments/medications available for atherosclerotic disease. It made no misleading claims with regard to safety or efficacy and therefore could not be construed as raising false hopes. For these reasons the companies submitted that the press pack was not in breach of Clause 7.2. The supplementary information to Clause 20.2 allowed for the provision of non-promotional information about prescription medicines to the general public via press announcements, or in response to enquiries from journalists etc, on the condition that this information was factual, balanced and not designed to encourage members of the public to ask their doctors to prescribe a specific medicine. As already mentioned, the press pack fulfilled all of these requirements and therefore was not in breach of Clause 20.2. Since Clause 20.2 allowed provision of non-promotional information to the public, subject to the above constraints, and since the companies did not commission the article in The Times, the companies did not consider that they were in breach of Clause 20.1 either. A list of journalists to whom the press pack had been sent was provided.

PANEL RULING

The Panel noted that complaints about items in the media were judged on the information provided by the pharmaceutical company or its agent to the journalists.

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the general public and medicines which, although not prescription only, might not legally be advertised 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 Panel examined the press information pack. It contained a news release, a programme for the press briefing which was held on 8 September 1998, three background documents, one on the CAPRIE study, one on vascular disease and its relation to myocardial infarction (MI), ischaemic stroke, and peripheral vascular disease (PVD) and one on the management of MI, stroke and PVD. The press information pack also included a Plavix Fact Sheet, a reprint of the CAPRIE paper, a Plavix summary of product characteristics (SPC), details of the agreement between Sanofi Winthrop and Bristol-Myers Squibb and four 35mm slides.

The Panel noted the indication for Plavix was for the reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from 7 days until less than 6 months), myocardial infarction (from a few days until less than 35 days) or established peripheral arterial disease.

The Panel considered that the press information pack gave very detailed information about the indication for Plavix. There was no claim in the press information pack that Plavix prevented strokes. The press information pack referred to the combined endpoint of myocardial infarction, ischaemic stroke and vascular death. The press information pack was not misleading in this regard.

The Panel noted that the statement in the news release that 'Plavix prevents an estimated 26% more events than aspirin' was followed by an asterisk. The explanation for the asterisk appeared at the end of the news release. The calculation was based on the results of the CAPRIE study of a relative risk reduction of 8.7% in favour of Plavix. If the data from the Antiplatelet Trialists' Collaboration, which showed that aspirin prevented 25% of vascular events compared to no treatment/placebo, was extrapolated to the CAPRIE population, this would represent an additional 26% reduction in the number of events prevented with Plavix versus aspirin.

The Panel noted that the CAPRIE study referred to the established data of a 25% relative risk reduction in the number of events accepted to be provided by aspirin and that in a patient population similar to CAPRIE, aspirin would be expected to prevent about 19 major clinical events versus 24 with clopidogrel for each 1000 patients treated for one year.

The Panel noted that the newspaper article stated, when referring to the CAPRIE study, that 'It showed that Plavix prevented an estimated 26 per cent of instances of serious trouble in people who had already had a history of strokes'. Backgrounder 1 printed in bold the claim 'This represents an additional 26% reduction in the number of events prevented with Plavix versus aspirin'. A similar claim was in printed in bold in the Fact Sheet. The Panel considered that given the prominence attached to these claims, the press materials could have been clearer with regard to the calculation of the figure of 26% which was calculated using an extrapolation from a meta analysis and related to vascular events not simply stroke.

The Panel did not consider that the press information pack constituted an advertisement for a prescription only medicine to the general public as alleged. No breach of Clause 20.1 of the Code was ruled. On balance the press information pack was not unreasonable in relation to the requirements of Clause 20.2 of the Code. No breach of that clause was ruled.

APPEAL BY COMPLAINANT

The complainant considered the Panel's statement 'The article was not solicited etc', was very surprising considering the further statement 'Press packs had, however, been made available'.

If it was not against the Code for the issuing of press packs to quality broadsheets to produce an article which had not been corrected by the issue of that press pack, then, in the complainant's opinion, it most certainly ought to be.

The complainant provided a copy of a letter from a local consultant cardiologist which stated that the main concern was whether the information provided was balanced. The Panel ruling did acknowledge that the press materials could have been clearer. The consultant had not seen the packs but the excerpts mentioned in the Panel ruling were certainly misleading in part.

The consultant stated that the differentiation of absolute and relative risk was very important in appreciating benefit. Talking about an additional 26% reduction in the number of events prevented with Plavix versus aspirin sounded impressive but, in reality based on the CAPRIE study, this only meant five major events per 1000 patients treated for one year. Furthermore, there was no difference in mortality. The only subset in which there was statistical benefit of clopidogrel over aspirin was that with peripheral vascular disease.

The other criticism was that there was just one randomised trial comparing clopidogrel to aspirin.

The consultant's view was that new and expensive medical developments should be assessed at a national level by an independent and expert body (NICE) before deciding whether or not they should be funded/prescribed on the NHS. Such decisions should be kept under regular review. Pressure should not be put on local GPs and consultants through patients demanding such care. It was time that the Government was explicit about rationing of health care. Only national guidelines would achieve this.

RESPONSE

Bristol-Myers Squibb and Sanofi Winthrop responded to the concerns of the complainant and the consultant cardiologist in turn.

Complainant

Bristol-Myers Squibb and Sanofi stated that the press releases were focused on the medical and scientific press. Press information packs were only released to non-scientific media following a specific request from a journalist and in total only three packs were released to such journalists (The Times, The Investors Chronicle and Healthcare Plus). Making press information packs available 'on request' did not constitute solicitation.

The complainant's use of the word 'issuing' implied that the press information packs were distributed, unsolicited, to various broadsheets. This was not the case. As mentioned previously, press information packs were only made available to non-scientific media following a specific request from an interested journalist. By applying this restriction the companies were able to ensure that press information packs were only sent to responsible journalists from quality papers and, in fact, only one broadsheet (The Times) received a press information pack.

The companies referred to the supplementary information to Clause 20.2 of the Code. This allowed for the provision of non-promotional information about prescription medicines to the general public via press announcements or in response to enquiries from journalists etc on the condition that the information was factual, balanced and not designed to encourage members of the public to ask their doctors to prescribe a specific medicine. As explained in the companies' initial response the press information pack was a balanced, objective and up to date presentation of the evidence concerning both clopidogrel and the other treatments/medications available for atherosclerotic vascular disease. It made no misleading claims with regard to safety or efficacy and information was not presented in a fashion that would encourage members of the public to seek prescription of clopidogrel from their GP. The companies, therefore, believed that the press information pack fell well within the constraints of Clause 20.2. The companies had no jurisdiction over the contents of articles written by independent journalists and should not be held responsible for any 'corrections' that should have been made to such articles prior to publication.

Consultant Cardiologist

The companies stated that the thrust of this complaint concerned the consultant's belief that the presentation of the benefits of clopidogrel over aspirin within the press information pack was misleading.

The consultant stated that talking about an additional 26% reduction in the number of events prevented with Plavix vs aspirin sounded impressive but, in reality, based on CAPRIE, this only meant five major events per 1000 patients treated for one year.

The consultant suggested that the companies had tried to disguise the size of the benefit of clopidogrel over aspirin, in terms of absolute number of events prevented, by presenting only 26% figure. This was not the case. All items in the press information pack that contained the 26% figure also clearly portrayed the data in terms of absolute numbers of events prevented and the latter was contained in the sentence immediately preceding the 26% claim. The format adopted in the press information pack used words to the effect of:

'Extrapolating this to the CAPRIE study, it is estimated that Plavix will prevent 24 events per year compared to 19 events per 1000 patients per year with

aspirin. This represents an additional 26% reduction in events with Plavix v aspirin.'

Presenting the relative (percentage) and absolute data in an adjacent fashion such as this left the reader in no doubt as to the absolute benefits of clopidogrel over aspirin.

With regard to the view that there was no difference in mortality demonstrated in CAPRIE, the companies stated that CAPRIE contained a single primary end-point, which was the composite of myocardial infarction, ischaemic stroke, and vascular death. Clopidogrel was proven to confer an 8.7% relative risk reduction over aspirin for prevention of this end-point in patients with recent myocardial infarction (from a few days until less than 35 days), recent ischaemic stroke (from seven days until less than six months), or established atherosclerotic peripheral vascular disease. The difference was statistically significant (p=0.043) and it was based upon this finding that the worldwide licence had been granted. The companies made no claims for clopidogrel in terms of all-cause mortality therefore the complainant's statement was irrelevant. Notwithstanding this, in CAPRIE clopidogrel was compared with an active comparator, ie aspirin. There was no placebo group This active comparator had already been shown to reduce all-cause mortality considerably. It was therefore not surprising that the difference in all-cause mortality did not reach statistical significance. In addition, clopidogrel was not expected to reduce death due to non-vascular causes. Since a large proportion (30%) of the deaths in CAPRIE were non-vascular in origin, one would not expect to see a statistically significant difference in all-cause mortality. Despite this, there was a trend towards improved all-cause mortality in clopidogrel treated patients (3.05% with clopidogrel versus 3.11% with aspirin).

With regard to the view that the only subset in which there was a statistical benefit of clopidogrel over aspirin was peripheral vascular disease, the companies stated that CAPRIE was not adequately powered for statistical analysis of the individual subgroups therefore no meaningful conclusion could be drawn from such analysis. This was clearly the conclusion of the US Food and Drug Administration (FDA) and the European Medicines Evaluation Agency, both of which had approved clopidogrel for the full spectrum of patients included in CAPRIE.

The companies submitted that the number of studies conducted on clopidogrel did not fall within the jurisdiction of the Code. The companies' responsibility under Clauses 7.2 and 7.3 was to ensure that information, claims and comparisons were accurate, balanced, fair, objective, unambiguous, based on an up to date evaluation of all the evidence and capable of substantiation. As explained in detail in the response to the Panel the press information pack complied with these requirements in full.

Notwithstanding this, CAPRIE was the largest clinical trial ever conducted on a medicine in development. It recruited over 19,000 patients and followed them up for up to 3 years. All groups were well matched and were representative of a 'real life' population in terms of co-existing diseases (eg hyperlipidaemia, hypertension, diabetes, smoking etc) and concomitant medications. In addition there was an independent steering committee. The result was a high quality study with robust data and sound conclusions. The validity of the findings was reflected both by its publication in The Lancet and by the FDA's decision to licence clopidogrel based on the result of this single study when it was its usual practice to insist on two studies before a licence was granted.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant considered that the industry had an absolute responsibility to ensure that publications about its products in the lay press did not encourage inappropriate GP consultations.

It was vital that the industry respected the fact that the NHS budget was limited and that it started to take a more responsible attitude to this very basic fact of general medicine in the UK.

In policing itself it seemed inappropriate that there were no statisticians judging the efficacy of a medicine who had no vested interest whatever the outcome. Unless more rigorous self-policing of such articles occurred, there was a strong case for urgent Government intervention.

APPEAL BOARD RULING

The Appeal Board noted that under the Code companies were permitted to issue materials to the press. Complaints about articles in the press or other media were judged on the information provided by the pharmaceutical company or its agent. Rulings were not based on the article itself.

The Appeal Board examined the Plavix SPC. The product was indicated for the reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined by ischaemic stroke (from 7 days until less than 6 months), myocardial infarction (from a few days until less than 35 days) or established peripheral arterial disease. The SPC stated that the indication was based on the results of the CAPRIE study comparing clopidogrel with [aspirin] and that the slight but statistically significant difference of clopidogrel over [aspirin] was mainly related to patients enrolled due to peripheral arterial disease.

The Appeal Board noted that Section 5.1 of the SPC stated that since the CAPRIE study was not powered to evaluate efficacy of individual subgroups, it was not clear whether the differences in relative risk reduction across qualifying conditions were real, or a result of chance.

The Appeal Board considered that the article in The Times about Plavix was inaccurate. It referred to a tablet a day to ward off strokes when the indication for Plavix was for the reduction of atherosclerotic events. Further the article referred to Plavix preventing an estimated 26% of instances of serious trouble in people who had a history of strokes and advanced coronary artery disease.

The Appeal Board noted how the 26% figure had been calculated. The CAPRIE study showed that patients

treated with aspirin experienced 58 vascular events per 1,000 patients per year, compared to 53 with Plavix, a statistically significant relative risk reduction of 8.7%. Data from the Antiplatelet Trialists' Collaboration (which showed that aspirin prevented 25% of vascular events compared with no treatment/placebo) was then extrapolated to the CAPRIE population. This would equate to the prevention of 24 events per 1000 patients per year with Plavix compared with 19 events with aspirin and this represented an additional 26% reduction in the number of events prevented with Plavix versus aspirin.

The Appeal Board noted that the Plavix press information pack was aimed at the medical/scientific press but a small number had been requested by, and supplied to, members of the lay press. The news release began by stating the patient population for which Plavix was indicated and then stated at the end of the first paragraph on page 1 that 'Plavix prevents an estimated 26% more events than aspirin*'. The asterisk referred the reader to the 'Editors note' on page 3 in which it was explained that the figure of 26% had been calculated by extrapolating the results from the Antiplatelet Trialists' Collaboration data to the CAPRIE population. In the more technically detailed fact sheet and backgrounders the figure of 26% and the explanation of its derivation were given in the same paragraph.

The Appeal Board was concerned about the basis for the claim in the press information pack that Plavix prevented an additional 26% in the number of events compared to aspirin. The extrapolation of results from the Antiplatelet Trialists' Collaboration data to the CAPRIE study assumed that the two patient populations were comparable. The Appeal Board considered that it was not appropriate at this stage to assume that this was so. The Appeal Board noted the caveats in the SPC regarding the CAPRIE data referred to above. The Appeal Board considered that the press information pack was misleading and ruled breaches of Clauses 7.2 and 20.2 of the Code.

The appeal was successful.

Complaint received **29 October 1998**

Case completed **14 April 1999**

CASE AUTH/786/11/98

CONSULTANT'S WIFE v SEARLE

Conduct of a representative

The wife of a hospital consultant complained about the activities of a Searle representative, alleging that her attendance and behaviour at the hospital where the complainant's husband was employed had attracted widespread attention and comment about her unprofessional conduct. It was alleged that the representative had visited the complainant's husband in his office on innumerable occasions and he had received a plethora of gifts, exceeding the recommendation in the Code. It was also alleged that it was the representative's habit to regularly entertain a selected group of doctors at the hospital together with a medical secretary. She lavished hospitality way beyond the spirit of the Code. The complainant believed that the representative had used her position to gain access to the hospital where she promoted her relationship with the complainant's husband which had resulted in the breakdown of the complainant's marriage.

The Panel noted that, counting both calls and meetings, the representative had seen the consultant twelve times in six months in 1996, twenty times in 1997 and three times in 1998. Searle commented on the reasons for this and provided a printout of the representative's visits. The Panel noted the requirement of the Code that representatives must ensure that the frequency, timing and duration of calls on health professionals and the like, together with the manner in which they were made, did not cause inconvenience. The number of calls made on a doctor by a representative each year should not normally exceed three on average. This did not include the following which might be additional to those three visits: attendance at group meetings, including audio-visual presentations and the like; a visit which was requested by a doctor or a call which was made in order to respond to a specific enquiry; a visit to follow up a report of an adverse action. The Panel noted that the consultant had requested some of the visits. The Panel considered that it would have been helpful if the printout had included more details so that the nature of each visit was made clear. The Panel considered that, in the circumstances, there was no breach of the Code in relation to the number of calls and ruled accordingly.

The Panel noted that the Code required promotional aids to be inexpensive and relevant to the recipient's profession or employment. Inexpensive meant costing the donor company no more than £5 excluding VAT. There was no limit to the number of promotional aids that might be given. The Panel noted that the promotional aids listed by Searle had each cost the company less than £5 excluding VAT and no breach of the Code was ruled.

The Panel noted that two meetings described by Searle had taken place in local restaurants. The first had involved seven health professionals and the representative at a cost of approximately £40 per head. The second had involved three of the health professionals who had attended the first, together with the surgical team secretary and the representative, at a cost of approximately £32 per head. The Panel considered that the meetings had limited educational content. The Panel did not accept that the nature of the meetings justified the associated hospitality. The Panel queried whether the cost of the meals was in excess of what the

recipients might normally adopt when paying for themselves. In the Panel's view, the meetings were inappropriate as they consisted of discussions in a public restaurant, the hospitality was not secondary to the main purpose of the meetings and it was inappropriate for the surgical team secretary to have attended the second meeting. The Panel therefore ruled a breach of the Code. The Panel also considered that, in relation to the requirements of the Code, the representative, by arranging the meetings, had failed to maintain a high standard of ethical conduct and comply with all the relevant requirements of the Code. A breach of the Code was ruled.

The wife of a hospital consultant complained about the activities of a representative of Searle. The complainant submitted a formal letter of complaint which was accompanied by a copy of a letter which she had sent direct to Searle detailing her allegations.

COMPLAINT

The complainant alleged that the representative had been blatantly in breach of the Code. Her attendance and behaviour at the hospital at which the complainant's husband was employed as a consultant had attracted widespread attention and comment regarding her unprofessional conduct.

The Code clearly stated: Clause 15.2 – 'Representatives must at all times maintain a high standard of ethical conduct in the discharge of their duties and must comply with all relevant requirements of the Code'.

The representative had visited the complainant's husband in his office on innumerable occasions contrary to Clause 15.4 of the Code. The supplementary information to Clause 19.1 stated: "A useful criterion in determining whether the arrangements for any meeting are acceptable is to apply the question 'would you and your company be willing to have these arrangements generally known?'"

The complainant stated that it transpired that her husband had received a plethora of gifts including a number of telephone cards marked Arthrotec 15, exceeding the generous recommendation of Clause 18.2 of the Code. A list of gifts could be supplied on request.

The complainant said that the representative had the reputation of being a very generous hostess to her friends. Clause 19 clearly stated that 'Companies are permitted 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. The level of the hospitality must be appropriate and not out of proportion to the occasion…' It was the representative's habit to regularly entertain a select group of doctors from the hospital and a medical secretary who was a friend of the representative and a very close friend of one of the doctors within the group. She lavished hospitality way beyond the spirit of the Code.

The complainant genuinely believed that the representative had used her position to gain access to the hospital, where she abused the facility of Searle to promote her relationship with the complainant's husband, which had resulted in the breakdown of their marriage.

The complainant had been heartened by support given to her by the local medical community and she felt that the consequences of the representative's behaviour would have widespread repercussions.

The complainant stated that all of the accusations could be substantiated upon request.

Was it Searle's wish that its ethical image be portrayed by the actions of this employee?

The complainant had copied her letter of complaint to the chief executive of her husband's employing NHS Trust.

The complainant subsequently sent the Authority a copy of the further letter which she had sent to Searle in response to its request for details of the gifts which her husband had received from the representative.

The complainant stated that had she known the significance of the developing relationship between her husband and the representative, she would have taken a much greater interest in those gifts bearing Searle's identity that her husband brought home. The complainant could say with certainty that over the past months her husband had received a number of telephone cards, a lamp, a stethoscope, more than one fire extinguisher, more than one instrument for cutting seat belts, a sports bag, a mouse mat with calculator, some small towels and a host of other small items. The complainant stated that she could not comment on any gifts or favours to which she had not been made privy. The complainant was no longer in possession of these gifts.

RESPONSE

Searle said that it regarded any complaint about one of its representatives as a serious matter and had conducted a thorough investigation of the representative's activity records and expense records. For the purpose of responding to the complaint it had focused on the period spanning the past 12 months.

The lady in question had worked as a field representative for Searle for over eleven years. She was both well regarded and well known by the health professionals in her territory having always worked in the same area. She currently worked as a hospital specialist. In 1987 she passed the ABPI representatives examination with distinction. There had never been any previous complaint about her conduct during the time she had been employed by Searle.

All Searle representatives were conversant with the requirements of the Code. Each representative received comprehensive training in head office by a member of the medical information and regulatory affairs department. It was an internal requirement that the trainers had completed the Code of Practice Authority's training session on the Code. At the internal training course each representative was given

a current copy of the Code together with a handout of the acetates used in the session, copies of which were provided. Any revisions to the Code which involved the representatives' activities were communicated to the field force on an ongoing basis and a copy of the revised Code was provided.

Clause 15.4 Frequency, timing and duration of calls – The complainant alleged that Searle's representative visited the consultant on innumerable occasions contrary to Clause 15.4 of the Code.

Searle operated an electronic territory management system (ETMS) for recording representatives' activities. Each representative recorded their daily activities including face to face calls on health professionals, audio-visual meetings, group meetings etc. While the information was recorded by each representative it was in the individual's own interest to record the information accurately since it was used as the basis for assessment of achievements against targets. A printout from the ETMS for representatives' activities which over the last 12 months included the consultant was provided.

The printout showed that in the last 12 months the representative had made face to face calls with the consultant at the hospital on four occasions, the dates being provided to the Authority. This frequency of calling was within the requirements of the Code. Furthermore, it was of relevance that the consultant had not complained about the frequency of the calls. Searle therefore denied any breach of Clause 15.4.

In response to a request for further information, details of all visits since 7 June 1996 were provided. The records showed that between June 1996 and December 1996 ten calls were made and two meetings were held. In 1997 thirteen calls were made, one of which was listed as a call with delivery item, and seven meetings were held. In each instance the consultant's name was given.

Searle provided a letter from the consultant to substantiate the submission that the representative at all times maintained a high standard of ethical conduct in the discharge of her duties. While the supplementary information to Clause 15.4 of the Code suggested that the number of calls should not normally exceed three on average each year, it was clear that in the case in question there was good legitimate reason for more frequent visits over the time period in question. During this time period the company expanded the relevant health product range from two to ten products and added two new forms of the analgesic Zydol, all of these being products relevant to the consultant and all requiring addition to the hospital formulary to secure prescribing within the hospital. In his position as a consultant, he would have been instrumental in leading the requests for formulary approval.

The representative was involved in a range of activities which included: discussion and provision of product information to update the hospital formulary, formal slide and video presentations, contribution to educational and training sessions, and loan of the company pelvic models for practical training sessions. Each loan would involve two visits, one for delivery and another for collection, since such loans were provided on a short term basis.

It was relevant that the consultant indicated in his letter that the above range of activities, '…necessitated an increase in the number of visits over and above that which one would normally associate purely with product information. A certain number of these visits would, of course, have been at my invitation and those of our department. There has been no suggestion by any of the hospital based personnel that these were inappropriate or obtrusive.'

Clause 18 Gifts and inducements – The complainant alleged that the consultant received a 'plethora' of gifts from Searle's representative which exceeded the recommendations made in Clause 18.2.

Decisions on type and allocation of promotional aids for representatives were taken in head office. Individual representatives had no budget for such items. All such items were approved for use through the standard internal procedure and required regulatory and medical sign off.

A list of the promotional aids (gifts) supplied to Searle representatives during 1998 was provided. This indicated the cost of each item and the quantity allocated to each representative for each promotional cycle. As required by Clause 18.2 no item cost more that £5. None of the items constituted a competition prize. An example of each gift was provided.

In the complainant's second letter she listed 'telephone cards, a lamp, a stethoscope, more than one fire extinguisher, more than one instrument for cutting seat belts, a sports bag, a mouse mat with calculator, some small towels' as items that she alleged had been provided for her husband by Searle's representative. Of these, telephone cards and a stethoscope had been supplied to representatives in the past 12 months. In previous years Searle had provided a desk lamp, a car fire extinguisher, seat belt cutter, mouse mat, calculator and surgery hand towels. It had not provided a sports bag as a promotional aid.

In all instances promotional aids would have cost less than £5. Searle did not believe that any of the promotional aids provided or their cost breached Clause 18.2.

In response to a request for the representative's recollection of the promotional aids supplied to the consultant, Searle stated that the representative had not kept any records of the items left and there was no requirements for her to do so since such items comprised branding aids and records were held centrally. In response to the specific question as to what the representative recollected leaving with the consultant she listed the following: desk fan; fire extinguisher (car); desk tidy; patient education pads; desk diary; stethoscope; pads and pens.

Clause 19 Hospitality and meetings – Searle's representative had held two meetings in the last twelve months which included the consultant. One in December 1997 and the second in April 1998. Only the former was recorded on the ETMS printout (which was provided); on the other date there was a system shutdown.

December 1997 – Details of those at the meeting were provided. Hospitality for the seven health

professionals present at the meeting and the representative was provided at a local restaurant at a total cost of £322.70.

April 1998 – Details of those at the meeting was provided. Hospitality was provided at a local restaurant for those present at the meeting, three health professionals, the surgical team secretary and the representative at a total cost of £162.42.

The purpose of each of the two meetings was to negotiate and secure hospital formulary listing of a new form of Zydol, the soluble tablet, and to follow-up early experience once it gained formulary acceptance, which was early in 1998. Copies of agendas were not available. The level of hospitality was not out of proportion to the occasion and the cost was of a level that recipients would normally pay for themselves. Searle therefore did not believe these activities breached Clause 19.

Details of the annual budget allocated to each representative for promotional meetings in 1998 were provided. In the 12 months to November 1998, the representative in question had spent 60% of the budget. This was not consistent with the complainant's allegations that she 'lavishes hospitality'.

Representatives' expenditure was checked and signed off by their line managers in accordance with the company signatory policy. Receipts had to accompany any expense claim and approval by the cost centre manager was mandatory for reimbursement.

In response to a request for more information about the meetings, Searle explained that each meeting was held in the restaurant but not in a private room. The meeting in April 1998 was held between 8pm and 11pm. The meeting in December 1997 was held between 1.30pm and 3.30pm. No further details of timetables were available. The surgical team secretary attended as an integral part of the departmental team as the person who had been fully involved and been responsible for all the administrative matters related to all the formulary discussions and applications. On both occasions these meetings comprised one of a series of ongoing discussions and negotiations culminating in the inclusion of a Searle product on the hospital formulary.

In conclusion, the representative had, Searle believed, conducted her company activities in full compliance with the Code. She had always maintained a high standard of ethical conduct in the discharge of her duties which was reinforced in the letter from the consultant. There had not been any complaint made by either the consultant, by his team or by any other health professional in the hospital. It was therefore regrettable that the representative was the subject of a complaint emanating from a source that was connected only indirectly and inadvertently to her professional activities as a representative. The company denied any breach of Clause 15.2.

PANEL RULING

The Panel noted that the representative had made a number of visits to the consultant. Twelve visits in six months in 1996, twenty visits in 1997 and three in 1998. The Panel noted the requirements of Clause 15.4 of the Code that representatives must ensure that the frequency, timing and duration of calls on health professionals, and the like, together with the manner in which they are made, did not cause inconvenience. The supplementary information to that clause gave guidance that companies should arrange that intervals between visits did not cause inconvenience. The number of calls made on a doctor by a representative each year should not normally exceed three on average. This did not include the following which might be additional to those three visits: attendance at group meetings, including audio-visual presentations and the like; a visit which was requested by a doctor or a call which was made in order to respond to a specific enquiry; a visit to follow up a report of an adverse action.

The Panel noted that the consultant had requested some of the visits. The Panel also noted the submission from the company. The Panel considered that it would have been helpful if the printout of the representative's visits had included more details so that the nature of each visit was made clear. The Panel considered that in the circumstances there was no breach of Clause 15.4 of the Code and ruled accordingly.

The Panel examined the promotional aids provided by Searle. Clause 18.2 of the Code stated that promotional aids had to be inexpensive and relevant to the recipient's profession or employment. Inexpensive was defined as costing the donor company no more than £5, excluding VAT. There was no limit in Clause 18.2 as to the number of promotional aids that could be given. The Panel noted that the promotional aids listed by Searle had cost the company less than £5 excluding VAT. The Panel ruled no breach of the Code. The Panel did not examine and approve each promotional aid as far as relevance to the practice of medicine as this was not the subject of the allegation which focused on cost. The Panel was nevertheless concerned that Searle had supplied a road atlas in cycle 3 of the year when this was specifically mentioned as not being allowed in the supplementary information to Clause 18.2 of the Code. In addition the Panel noted that a box of tissues incorporated a competition which did not appear to be a *bona fide* test of skill. The Panel considered that these two matters should be taken up with Searle under the provisions of Paragraph 16 of the Constitution and Procedure. The Panel noted that an Easter chick logo bug, a CD Rom case and a credit card wallet had been supplied as promotional aids. The Panel queried the relevance of these items to the practice of medicine and requested that Searle be advised of its views.

The Panel noted that the meetings held in December 1997 and April 1998 had taken place in local restaurants. The meeting on December, from 1.30 – 3.30pm, had involved seven health professionals and the representative at a cost of approximately £40 per head. The meeting in April 1998, from 8 – 11pm, had involved three of the health professionals who had attended the December meeting and the surgical team secretary together with the representative at a cost of

approximately £32 per head. The Panel noted that the Code permitted companies to provide hospitality within certain parameters as set out in Clause 19, which stated that 'The level of hospitality offered must be appropriate and not out of proportion to the occasion and the costs involved must not exceed the level which the recipients would normally adopt when paying for themselves'. The Panel also noted the supplementary information to Clause 19 which set out certain basic principles for any meeting: the meeting must have a clear educational content, the hospitality associated with the meeting must be secondary to the nature of the meeting and must be appropriate and not out of proportion to the occasion and that any hospitality provided must not extend to spouses and other persons unless that person qualified as a proper delegate or participant at the meeting in their own right. Administrative staff might be invited to meetings where appropriate. Further, the Panel noted that the supplementary information to Clause 19 also stated that 'The impression that is created by the arrangements for any meeting must always be kept in mind'.

The Panel was concerned that the surgical team secretary had attended the December meeting. The purpose of the meeting was to negotiate and secure hospital formulary listing for Zydol Soluble. It appeared that Zydol was already on the hospital for formulary. In the Panel's view the meeting related to clinical matters and not administrative matters and it was inappropriate for the surgical team secretary to attend.

The Panel considered that the meetings had limited educational content. The Panel did not accept that the nature of the meetings justified the associated hospitality. The Panel queried whether the cost of the meals were in excess of what the recipients might normally adopt when paying for themselves. In the Panel's view, the meetings were inappropriate as they consisted of discussions in a public restaurant, the hospitality was not secondary to the main purpose of the meetings and it was inappropriate for the surgical team secretary to attend. The Panel therefore ruled a breach of Clause 19 of the Code.

The Panel also considered that in relation to the requirements of the Code, the representative, by arranging the meetings, had failed to maintain a high standard of ethical conduct and comply with all the relevant requirements of the Code. A breach of Clause 15.2 of the Code was ruled.

Complaint received **2 November 1998**

Case completed **27 January 1999**

CASE AUTH/787/11/98 *NO BREACH OF THE CODE*

ANON v GLAXO WELLCOME

Joint Serevent Incentive Scheme

An anonymous complainant sent in a field force circular issued by Glaxo Wellcome, stating that it offered a bonus for seeing general practitioners four to seven times in the last three months of 1998, some of them seen previously to this, and alleging that this was in breach of the Code.

The Panel noted that the Code stated that representatives must ensure that the frequency, timing and duration of calls did not cause inconvenience. The number of calls made on a doctor by a representative each year should not normally exceed three on average. This did not include the following which might be additional to those three visits: attendance at group meetings, including audio-visual presentations and the like; a visit which was requested by a doctor or a call which was made in order to respond to a specific enquiry; a visit to follow up a report of an adverse reaction. The number of calls made on a doctor by a representative was interpreted as being calls by one individual representative and not as calls by representatives promoting one particular medicine. In the Panel's view it was possible in theory for a company to have a number of representatives promoting its products and each representative could call on the same doctor three times a year.

The Panel noted from Glaxo Wellcome's response that representatives were asked to increase the number of doctors whom they had seen four or more times in a one year period. The Panel noted that the average contact frequency for the last 12 months was 3.4 for Serevent target doctors and 3.0 for all customers. It further noted that 47% of contacts were meetings which made the frequency of calls much less than three on average.

The Panel considered that there was no evidence that any individual representative had visited any particular doctor more than three times in one year or that the intervals between successive visits had been inappropriate. The Panel therefore ruled no breach of the Code in that regard.

The Panel noted that the documentation made no reference to seven visits, as mentioned by the complainant. The Panel considered that the details of the scheme advocated a course of action, ie four or more contacts, which might be visits to individual doctors that would be in breach of the Code. The Panel considered that the failure to present the incentive scheme within the context of the requirements of the Code meant that a high standard had not been maintained. A breach of the Code was ruled.

Upon appeal by Glaxo Wellcome, the Appeal Board noted that the incentive scheme involved two different sales forces both promoting Serevent. The objective was that, between them, the two sales forces should increase the number of GPs that they moved into the four contacts and above category. The supplementary information to the Code stated that 'The number of calls made on a doctor by a

representative each year should not normally exceed three on average'. If two representatives were each promoting Serevent each of them could thus call on to a doctor three times in any one year to promote the product.

The Appeal Board noted that the incentive scheme was based on 'contacts' with GPs. The Code and its supplementary information referred to 'calls'. The Appeal Board considered that there was a difference between calls and contacts. Calls were one to one meetings, usually in a doctor's surgery. Contacts included calls but could also be representatives talking to a doctor at a group meeting. Such additional meetings were exempt from the limit of three visits.

The Appeal Board noted that Glaxo Wellcome put considerable resources behind training, constantly updating and reminding its representatives on the requirements of the Code. In the Appeal Board's view it was not necessary to reiterate requirements of the Code each time the company outlined a new sales incentive. The target of the incentive scheme related to four or more contacts, not calls, and these were split between two sales forces. The Appeal Board did not accept that the company had failed to maintain high standards and no breach of the Code was ruled.

An anonymous complainant provided a copy of a field force circular on 'The Joint Serevent Incentive Scheme' which had been issued by Glaxo Wellcome UK Limited.

COMPLAINT

The complainant stated 'Enclosed is a field force circular offering bonus for seeing GPs 4-7 times in the last 3 months of 1998 (some seen previously to this). Surely this contravenes the ABPI Rules.'

When writing to Glaxo Wellcome the Authority drew attention to the requirements of Clauses 2, 9.1, 15.4 and 15.9 of the Code.

RESPONSE

Glaxo Wellcome denied any breach of the Code. The company stated that Serevent was promoted by a dedicated Allen & Hanburys field force, and the September MAT (moving annual total) of doctors seen four times or more related to that force. From September 1998, this field force had been augmented by a contract force, and this incentive scheme related to both field forces.

Glaxo Wellcome considered that it was important that the background to the scheme was fully understood, particularly in relation to the requirements of Clauses 15.4 and 15.9, and the following information was pertinent to that understanding.

a) It was important to note that the targets were on a MAT basis, and related to the number of doctors seen during the last 12 months, updated at the end of each quarter, and the frequency of contacts. Therefore, representatives were not being asked to increase the number of times a doctor was seen in the last three months of 1998 from four to seven times, nor to see doctors between 4-7 times in that period. Thus, the complainant had completely misunderstood the scheme.

b) Representatives were asked to increase the number of doctors whom they had seen four or more times in a one year period, that was greater coverage of doctors seen. Many of these contacts were made as calls to doctors and all such calls were made within the remit of Clause 15.4, in that they did not cause inconvenience and took into account the wishes of the doctors being called upon. Glaxo Wellcome had not had any complaints from doctors during this or previous campaigns, regarding the frequency at which representatives made calls upon them.

As well as calls requested by the representative, many calls were the result of a request from the doctor for such a visit, or to follow up an adverse reaction report, although at the present time Glaxo Wellcome did not have exact data regarding the breakdown between the two types of calls.

However, it was important to stress that another method of contact was at meetings, both in the practice premises and at academic centres and, of course, the doctor was a willing participant in such meetings.

c) The supplementary information to Clause 15.4 stated that the number of calls by a representative each year should not normally exceed three on average. This did not include attendance at group meetings, including audio-visual presentations or a visit requested by a doctor, or in response to a specific enquiry, or a follow up to an adverse drug reaction report.

Details of the number of customers seen by the Serevent sales force in the last year were provided:

At September 1998 the Allen & Hanburys' Serevent field force contact rates (MAT) showed an average contact frequency – all potential customers – of 2.6 for Serevent target doctors and 1.8 for total customers. Average contact frequency, excluding customers not seen during last 12 months, was 3.4 for Serevent target doctors and 3.0 for total customers. It had to be stressed that these were average 'all contact' rates and the figures for the average contact frequency across all potential customers made it clear why, across all general practitioners, there was a need to augment the present field force to increase promotional cover across all customers.

In relation to previous comments regarding the type and relevance of contact, 53% of contacts were calls and 47% were at meetings. Thus it could be seen that roughly one half of Allen & Hanburys' contacts were the result of meetings at the doctors' premises, which made the frequency of calls much less than three on average. Of course, within that average some individual doctors would be seen more than the average, for a number of reasons, but all with the doctors' agreement.

With regard to the incentive scheme in question Glaxo Wellcome provided the following details:

i) What were the representatives being asked to do?

- It could be seen from the background information that to even approach an average of three calls per

doctor per annum, a considerable increase in call rates to doctors' premises would be required.

- The scheme related to 'doctors seen', that was contacts and did not specify if this was at the doctors' premises or at meetings. From the information previously provided this split would be approximately 50:50.
- In the example shown in the field force circular, the goal was to increase the number of target doctors seen four or more times from 110 to 300.

The measurement criterion was the number of extra doctors seen divided by days available in the extended quarter September to December (120)

ie 300 minus 110 = 190.
190 divided by 120 = 1.58 extra doctors per day.

d) This was not an incentive to see the same group of doctors normally seen more often, and it was not clear where the complainant's assertion that the field force was being bonused for seeing GPs four to seven times in the last three months of 1998 was derived from.

e) It was quite clear from the circular that the scheme was based on maximising productive zone coverage for high potential and valued target GPs only.

The reward was for a number of GPs moved up into the four contacts and above category, thus bringing up the average contact rate across all potential customers.

ii) What were the rewards offered?

From the example previously referred to, if all targets were seen it would mean an extra 1.58 doctors per day being seen. Page four of the circular specified the amount of funding being paid into each business area team the nearer they came to target. Allocation to the contract representatives would be at the fixed amount per head specified, whilst other performance criteria would be taken into account for the full time Allen & Hanburys' Serevent team. Glaxo Wellcome therefore asserted that the scheme and the bonus were well within the spirit and meaning of Clause 15.4 and associated supplementary information.

With regard to Clause 15.9 of the Code, Glaxo Wellcome did not regard representatives' salary, activity and bonus schemes as coming within the remit of this clause and therefore material related to such schemes was not certified under this clause. The clause stated 'Companies must prepare detailed briefing material for medical representatives on the technical aspects of each medicine which they will promote'. Glaxo Wellcome considered the scheme did not involve technical aspects of Serevent and could not be regarded as briefing material thereon, which would require certification.

The briefing material provided did not advocate in any way any course of action which would be likely to lead to a breach of the Code by representatives.

All representatives received a presentation on their initial training course on the Code of Practice from a medical adviser. This was updated from time to time by further presentations. Compliance was stressed and each representative was provided with a copy of the Code. There was no specific written briefing material provided.

Glaxo Wellcome was also asked to consider Clause 9.1 of the Code: 'All material and activities must recognise the special nature of medicines and the professional standing of the audience to which they are directed, and must not be likely to cause offence. High standards must be maintained at all times'. From the foregoing explanation of actual call rates, Glaxo Wellcome considered that this clause had been upheld in all respects. Glaxo Wellcome had not received any complaints regarding the activities of its Serevent representatives, and although the complaint was anonymous, the company presumed from the material provided that a dissatisfied representative and not a doctor was the source.

Finally, Glaxo Wellcome did not accept that this incentive scheme was such as to bring discredit upon or reduce confidence in the pharmaceutical industry, and was not in breach of Clause 2. Such incentive schemes to increase call rates and coverage of customers were normal practice throughout the industry, and in this case the reward was not an undue proportion of regular fixed salary.

In conclusion Glaxo Wellcome considered this was a bona fide incentive scheme to increase coverage of the customer base and was not in breach of any clause of the Code.

PANEL RULING

The Panel noted that Clause 15.4 stated that representatives must ensure that the frequency, timing and duration of calls did not cause inconvenience. The supplementary information to Clause 15.4 stated that the number of calls made on a doctor and the intervals between successive visits were relevant to the determination of frequency. Companies should arrange that intervals between visits did not cause inconvenience. The number of calls made on a doctor by a representative each year should not normally exceed three on average. This did not include the following which might be additional to those three visits: attendance at group meetings, including audio-visual presentations and the like; a visit which was requested by a doctor or a call which was made in order to respond to a specific enquiry; a visit to follow up a report of an adverse reaction.

The number of calls made on a doctor by a representative was interpreted as being calls by one individual representative and not as calls by representatives promoting one particular medicine.

In the Panel's view it was possible in theory for a company to have a number of representatives promoting its products and each representative could call on the same doctor a maximum of three times a year. This would not include attendance at group meetings, requested visits, or calls to follow up specific enquiries or adverse drug reaction reports.

The Panel considered that the fact that Glaxo Wellcome had not had any complaints about frequency of visits did not mean that the arrangements were necessarily acceptable.

The Panel noted from Glaxo Wellcome's response that representatives were asked to increase the number of doctors whom they had seen four or more times in a one year period. The incentive scheme was to run from October to December 1998 and at the end of the year the December MAT would be compared to the September MAT to determine incentive payments due. The Panel noted that the average contact frequency for the last 12 months was 3.4 for Serevent target doctors and 3.0 for all customers. It further noted that 47% of contacts were meetings which made the frequency of calls much less than three on average.

The Panel considered that there was no evidence that any individual representative had visited any particular doctor more than three times in one year or that the intervals between successive visits had been inappropriate. The Panel therefore ruled no breach of Clause 15.4 of the Code.

The Panel was concerned about the details of the scheme. It had been provided with two A3 sheets. The documentation made no reference to seven visits, as mentioned by the complainant. It clearly encouraged representatives to contact doctors four or more times. Representatives were only to be rewarded for the number of high potential and valued GPs that they moved into the four contacts and above category. In the Panel's view representatives would have to contact doctors frequently to achieve these objectives within the last quarter of the year.

The Panel noted that Clause 15.9 of the Code required that companies prepare briefing material on the technical aspects of each medicine to be promoted. Further explanation of what briefing material consisted of was given in the supplementary information to Clause 15.9 which stated that the detailed briefing material consisted of both the training material used to instruct medical representatives about a medicine and the instructions given to them as to how the product should be promoted.

The Panel considered that the details of the scheme did not amount to briefing material on the technical aspects of Serevent. The Panel therefore ruled no breach of Clause 15.9 of the Code.

The Panel considered that the details of the scheme advocated a course of action, ie four or more contacts, which might be visits to individual doctors that would be in breach of the Code. The Panel considered that the failure to present the incentive scheme within the context of the requirements of Clause 15.4 of the Code meant that a high standard had not been maintained. A breach of Clause 9.1 of the Code was ruled.

The Panel was concerned that Glaxo Wellcome did not know how many calls were as a result of a follow up on adverse drug reaction reports.

The Panel did not accept that the scheme was in breach of Clause 2 and no breach of that Clause was ruled.

APPEAL BY GLAXO WELLCOME

Glaxo Wellcome was concerned that the Panel considered that it had failed to present the incentive scheme within the context of the requirements of Clause 15.4 of the Code and ruled a breach of Clause 9.1 of the Code.

Glaxo Wellcome stated that the basis of its appeal was as follows:

1 The company considered that the training and briefing of all representatives from the initial training onwards was to the highest standards.

2 Presentations were made on the Code in general and specifically on the requirements for representatives at training courses and at regular intervals thereafter, usually by medical advisers, or trained 'trainers'. This was followed by an examination. The requirements were also made clear on representatives' expectations (objective) documents. It was noteworthy that the representatives taking the ABPI examinations had a high pass rate, usually with high marks.

3 Each representative received a standard operating procedure, prepared by the medical and commercial directors, which specified the requirements of the Code and how representatives were required to work within the requirements. A copy of this document, last revised in August 1997, was provided. Glaxo Wellcome pointed out that the 'general requirements' demanded high standards.

4 Within this background, Glaxo Wellcome considered that each subsequent briefing did not need to have the requirements of the Code reiterated, high standards being implicit. There was certainly no evidence that offence to doctors had been claimed.

APPEAL BOARD RULING

The Appeal Board noted that, on joining Glaxo Wellcome, all representatives were trained on the requirements of the Code. In addition to receiving a copy of the Code representatives received an in-house document 'ABPI Code of Practice Guidelines for Representatives'. One section of the document was entitled 'Ensuring High Standards' and another detailed the requirements of Clause 15.4 regarding frequency, timing and duration of calls. The document had not been supplied to the Panel. Representatives also received regular reminders about the requirements of the Code.

The Appeal Board noted that the incentive scheme involved two different sales forces both promoting Serevent. The objective was that, between them, the two sales forces should increase the number of GPs that they moved into the four contacts and above category. The supplementary information to Clause 15.4 stated that 'The number of calls made on a doctor by a representative each year should not normally exceed three on average'. If two representatives were each promoting Serevent each of them could thus call on to a doctor three times in any one year to promote the product. In addition to the three calls each, the representatives could also see the doctor at group meetings, a visit requested by the doctor or made in order to respond to a specific enquiry and a visit to follow up a report of an adverse reaction.

The Appeal Board noted that the incentive scheme was based on 'contacts' with GPs. Clause 15.4 of the Code and its supplementary information referred to 'calls'. The Appeal Board considered that there was a difference between calls and contacts. Calls were one to one meetings, usually in a doctor's surgery. Contacts included calls but could also be representatives talking to a doctor at a group meeting. Such additional meetings were exempt from the limit of three visits allowed in the supplementary information to Clause 15.4.

The Appeal Board noted that Glaxo Wellcome put considerable resources behind training, constantly updating and reminding its representatives on the requirements of the Code. In the Appeal Board's view it was not necessary to reiterate requirements of the Code each time the company outlined a new sales incentive. The target of the incentive scheme related to four or more contacts, not calls, and these were split between two sales forces. The Appeal Board did not accept that the company had failed to maintain high standards and no breach of Clause 9.1 was ruled.

The appeal was successful.

Complaint received **2 November 1998**

Case completed **28 January 1999**

CASE AUTH/789/11/98

GLAXO WELLCOME v 3M HEALTH CARE

Promotion of Qvar

Glaxo Wellcome complained about a number of promotional items for Qvar issued by 3M Health Care. Qvar was a chlorofluorocarbon-free inhaler presentation of beclomethasone dipropionate (CFC-free BDP). Glaxo Wellcome marketed Becotide (CFC-BDP).

Glaxo Wellcome alleged that the data quoted in support of the message of increased deposition of CFC-free BDP compared with CFC-BDP was drawn from a healthy volunteer study but it was not labelled to make it clear that this was so. Such data must not mislead as to its significance. The Panel noted that data from patients with mild asthma treated with CFC-free BDP supported the volunteer data. Similar comparative data for CFC-BDP had not been supplied. In the Panel's view the use of healthy volunteer data where it was almost identical to clinical data was not necessary misleading. It was, however, assumed that data in promotional material referred to patients unless otherwise indicated and the absence of such labelling meant that the materials were misleading and a breach of the Code was ruled. Upon appeal by 3M Health Care in relation to certain of the promotional items, the Appeal Board noted that additional data had been supplied and considered that given that the data in patients and healthy volunteers was comparable, it was not unacceptable to present healthy volunteer data and the failure to label did not make it misleading. No breach of the Code was ruled.

Glaxo Wellcome alleged that the materials suggested that 800mcg CFC-free BDP had no effect on adrenal suppression and therefore that no patients receiving CFC-free BDP would experience problems with regard to systemic safety. Hypothalmic-pituitary-adrenal (HPA) function during corticosteroid therapy varied greatly from person to person and it could not be predicted which or how many patients might become HPA-deficient. The Panel noted that the materials cited by Glaxo Wellcome gave the impression that adrenal suppression was not a problem with Qvar. In the Panel's view this was not consistent with the summary of product characteristics (SPC) which referred to the possibility of BDP exerting detectable suppression of adrenal function and that systemic effects might occur. The Panel considered that the claims were misleading and did not reflect the available evidence. A breach of the Code was ruled.

Glaxo Wellcome stated that it was claimed that side effects such as hoarse voice and cough were lower with CFC-free BDP than with CFC-BDP. A bar chart which referred to patients with at least one treatment related adverse event showed statistically significant differences between Qvar and CFC-BDP. The study referenced, however, showed no significant differences between the treatments in respect of hoarse voice and cough. It was alleged that the material was misleading and did not reflect the evidence. The Panel considered that the claim 'In particular, inhalation-route problems like hoarse voice and cough were lower with Qvar (8% vs 12% $p < 0.042$)' suggested that there was a difference in the incidence of hoarse voice and cough for Qvar compared to CFC-BDP and this was not so. The Panel considered that the claim was misleading and did not accurately reflect the evidence. A breach of the Code was ruled. Upon appeal by 3M Health Care the Appeal Board accepted that the claim in the detail aid 'Low overall incidence of side effects' in relation to a 'Summary of safety data from five studies including measurements of dysphonia, cough and worsening asthma symptoms' was a statement of fact and not comparative like the other claims ruled in breach. The Appeal Board ruled no breach of the Code with regard to the detail aid.

Glaxo Wellcome alleged that the statement '…we have accepted relatively inefficient delivery systems with little or no question…' was neither accurate nor a fair reflection of the situation. As a result of extensive research by pharmaceutical companies, breath-actuated metered dose inhalers, large volume spacers and dry powder inhalers had been introduced specifically and successfully to address the issue of drug delivery. The statement disparaged the delivery devices of other pharmaceutical companies. The Panel noted the lung deposition data for the various products and devices. The Panel noted the context of the

statement and did not accept that it was disparaging to refer to accepting relatively inefficient delivery systems with little or no question provided that an acceptable clinical response was observed. The Panel ruled no breach of the Code.

The front cover of a patient information leaflet bore the statement 'Keeping you healthy in a healthier environment'. The same leaflet, under the heading 'The facts about your CFC-free asthma preventer inhaler (Qvar)', stated 'With CFC-containing inhalers most of the medicine goes to the mouth and throat, and only a little goes to the lungs. With Qvar, most of the medicine goes to the lungs where the medicine works to reduce inflammation.' Glaxo Wellcome stated that the unqualified statement on the front cover suggested that CFC-free BPD would keep the patient healthy, but this could not be predicted for every patient. The information might raise concerns with members of the public about other (CFC-containing) inhalers they might be using.

The Panel had some concerns about the statement 'Keeping you healthy in a healthier environment'. On balance, in the context of the brochure as a whole, the Panel did not consider that the statement would raise unfounded hopes of successful treatment as alleged. No breach of the Code was ruled. The Panel noted that the section headed 'The facts about your CFC-free asthma preventer inhaler (Qvar)' gave details of the differences in lung deposition between CFC-containing inhalers and Qvar. The Panel considered that the striking visual difference between a scintigram for the CFC-inhaler and that for Qvar would raise concern with members of the public about the CFC-inhalers they might have used or might still be using. Subsequent text explained the fact that with Qvar more of the medicine reached the lungs and so a lower dose of Qvar might be needed to get the same asthma control than with CFC-containing inhalers. The Panel considered that the section 'The facts about your CFC-free asthma preventer inhaler (Qvar)' with its reference to the deposition of CFC-inhalers was not a balanced presentation of the facts. It had not been explained in this section that, despite the fact that less medicine reached the lungs from CFC-inhalers, the dose for CFC-inhalers was set such that asthma was nonetheless controlled. The Panel ruled a breach of the Code. Upon appeal by 3M Health Care, the Appeal Board considered that the section was not a balanced presentation of the facts and upheld the Panel's ruling of a breach of the Code.

Glaxo Wellcome UK Limited complained about a number of promotional items for Qvar issued by 3M Health Care Limited. Qvar was a chlorofluorocarbon-free inhaler presentation of beclomethasone dipropionate (CFC-free BDP). Glaxo Wellcome marketed Becotide (CFC-BDP).

3M Health Care outlined the usage of the items at issue.

'Dear Doctor' letter (ref 0698/QV/004/009) This letter was sent to general practitioners together with a mail piece, a summary of product characteristics (SPC) and a reply paid card.

Product summary (ref 0498/QV/011/009) Transition to CFC-free inhalers involved all healthcare professionals. Therefore this item was intended to provide an overview of the product for distribution to the range of healthcare professionals, e.g. GPs, pharmacists (community and hospital), hospital doctors, independent pharmaceutical/medical advisers, nurses etc. Distribution (as appropriate to the customer's needs) was via the sales representative or other 3M contacts, e.g. medical information services.

Patient information leaflet (ref 0898/QV/042/002) This leaflet was only given to and discussed with the patient once the physician had made the decision to prescribe Qvar. It specifically related to Qvar and no other CFC-free inhaler. Again distribution as appropriate was to any healthcare professional who might be involved in the care of the patient during the transition phase.

Detail aid (ref 0398/QV/011/005) This item was used by the sales representative in one-to-one presentations of Qvar with healthcare professionals in secondary care only. The item was not left with the customer.

Slide pack (ref 0398/QV/011/002) This was primarily supplied to secondary care respiratory physicians together with a few primary care doctors with a special interest in asthma. It was designed to provide physicians with an information resource about Qvar which they could use in their own presentations should they wish to discuss it with other colleagues.

Glaxo Wellcome grouped its complaints where the same issue arose in different materials.

1 The use of research using healthy subjects extrapolated to support clinical effectiveness

On page one of the 'Dear Doctor' letter was a double scintigram entitled 'Lung-deposition of technetium-99m radio-labelled beclomethasone'. The scintigram was labelled to show that lung deposition of CFC-BDP was 4% and that of Qvar was 51%. Just below the scintigram was text which read 'Consequently, considerably lower doses of Qvar are required to achieve the same asthma control as CFC-BDP, which can only be good news for you and your patients'.

Page 5 of the product summary bore the same scintigram under the heading of 'Does Qvar reach the small airways?'

The Qvar patient information leaflet had the same scintigram although it bore no title.

Slide 32 in the Qvar slide pack was entitled 'Effectiveness α dose x efficiency'. A graph plotted the percentage of patients showing an improvement over baseline in FEV1 with Qvar 100mcg or CFC-BDP 100mcg. Next to the graph was the Qvar scintigram although it was not entitled or labelled in any way. The notes accompanying the slide did not refer to the scintigram.

COMPLAINT

Glaxo Wellcome stated that the data quoted in support of the message of increased deposition of

CFC-free BDP compared with CFC-BDP was drawn from a healthy volunteer study; there was no labelling to make it clear that this was so. Such data should not be used so as to mislead as to its significance. Glaxo Wellcome alleged a breach of Clause 7.2.

RESPONSE

3M Health Care stated that the scintigrams used in the 'Dear Doctor' letter represented the comparative deposition of Qvar and CFC-BDP in the same healthy volunteer in order to pictorially represent the results of the points discussed in the preceding paragraphs. The Leach (1998) paper from which the scintigram was taken also included data and a scintigram of lung deposition in a patient with asthma. High lung deposition (56%) with Qvar was also demonstrated in patients at similar values to those represented in the volunteer Qvar scintigram (51%). The second page of the letter (not referred to in this part of the complaint by Glaxo Wellcome) showed, in a clear and logical format, the clinical data which led from lung deposition of beclomethasone to clinical efficacy. 3M Health Care submitted that the presentation of the complaint (by omitting page 2) disregarded the context of the scintigrams.

Indeed, the SPC (which was enclosed with the mailer), Section 3.3, provided information about the improved deposition and the clinical benefits: 'Radio-labelled studies in patients with mild asthma have demonstrated that the majority of the drug (>55% ex-actuator) is deposited in the lung and a small amount (<35% ex-actuator) is deposited in the oropharynx. These delivery characteristics result in equivalent therapeutic effects at lower total daily doses of Qvar, compared with CFC beclomethasone dipropionate formulations'. Therefore no undue or unsubstantiated significance had been placed on this data and 3M Health Care did not consider it to be misleading.

In the Qvar product summary the volunteer deposition scintigraphs and the data values were similarly discussed and this was followed by a lead into the clinical trials data in terms of the hypothesis of improved lung deposition possibly allowing for a reduction in daily steroid dose with no loss of efficacy.

The justification for use in the patient information leaflet was equally valid. The scintigrams were included to pictorially illustrate that Qvar had a different lung deposition profile than the CFC-BDP products the patient had used previously. No comment or inference was made as to the likely clinical efficacy implications that these differences might have nor to the relationship between lung deposition and clinical efficacy. The leaflet was provided to the healthcare professional to supplement discussions about the new inhaler with the patient after the physician had decided to prescribe Qvar.

Slide 32, entitled 'Effectiveness α Dose x efficacy', summarised the data presented in preceding slides regarding the dose-response study. Pharmaceutical, deposition, pharmacokinetic and low dose efficacy data had already been presented to the reader at this point. The graph in slide 32 showed clear clinical effect data comparing 100mcg doses of Qvar and CFC-BDP. The scintigram (appearing earlier in slide 8) reappeared on this slide to serve as a reminder of the improved delivery of medicine to the lungs with Qvar.

3M Health Care submitted that scintigraphic images were commonly used to give a fair and balanced impression of drug deposition in the body. The presentation of such data, intimately linked with clinical trial data, provided accurate, balanced, fair, objective and unambiguous information to the reader and thus were not misleading.

PANEL RULING

The Panel noted that Qvar was indicated for prophylactic management of mild, moderate or severe asthma. The lung deposition data for Qvar in the study by Leach was from both healthy volunteers and mild asthmatics. The lung deposition data for CFC-BDP was only from healthy volunteers. The data from 12 healthy volunteers showed that for CFC-BDP lung deposition was 4% and oropharynx deposition was 94%. The comparable data for CFC-free BDP (Qvar) was 51% and 30%. The data from 16 patients with mild asthma showed that for CFC-free BDP lung deposition was 56% and oropharynx deposition was 28%.

The Panel noted the information in the Qvar SPC that >55% was deposited in the lung and a small amount <35% was deposited in the oropharynx.

The Panel noted that the data from patients with mild asthma supported the data from healthy volunteers for Qvar. The supplementary information to Clause 7.2 advised that the use of healthy volunteer data in promotional material should not mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there was data to show that it was of direct relevance and significance. The Panel noted that in this case lung deposition of CFC-free BDP in volunteers was similar to that in mild asthmatics (51% v 56%). Similar comparative data was not available for CFC-BDP. The Panel noted that no evidence had been presented to suggest that the lung deposition seen in healthy volunteers (4%) was not similar to that seen in patients. In the Panel's view the use of healthy volunteer data *per se*, where such data was almost identical to clinical data, was not necessarily misleading. The Panel noted, however, that it was assumed that the data in promotional material referred to the situation in patients unless otherwise indicated. None of the scintigrams referred to the fact that the data was from healthy volunteers and the absence of such labelling *per se* meant that the materials were misleading. A breach of Clause 7.2 of the Code was ruled. This ruling applied to all the items cited by Glaxo Wellcome in the complaint.

APPEAL BY 3M HEALTH CARE

3M Health Care noted that the Panel accepted that the Qvar deposition data, in patients, supported the images used in the promotional materials. Furthermore the Panel noted that there was no supportive evidence, in patients, for the volunteer data specifically referring to deposition of CFC-BDP.

With the exception of the 'Dear Doctor' letter and slide 32 of the slide pack, 3M Health Care wished to appeal the Panel's ruling. The 'Dear Doctor' letter was last used in October 1998 and would not be reissued. Slide 32, in which deposition data on Qvar in volunteers appeared alongside a graph of comparative efficacy, would be replaced as 3M Health Care agreed that this direct comparison of efficacy data from patients with deposition data from volunteers could be misleading. The replacement slide would only show the efficacy graph.

In support of its appeal, 3M Health Care provided data on file regarding the lung deposition values of CFC-BDP in a patient with asthma. As would be noted from the data supplied, this particular investigation was only one part of Study 1260-BRON. This study comprised three parts. As the 3M Health Care claims only referred to part of the study and also for reasons of confidentiality, it was only disclosing the results to Part 3 (which compared lung deposition of Qvar with CFC-BDP in a patient with asthma) as data on file. For completeness, 3M Health Care considered that the Appeal Board might find the description of the whole study, and the references therein, helpful.

3M Health Care considered that this data of lung deposition in a patient with asthma supported the differences between CFC-BDP and Qvar seen in the volunteer studies and thus the use of the volunteer data in the product summary and the patient information leaflet was not misleading.

The remaining argument, providing the Appeal Board accepted the data was the same for volunteers or patients, was the requirement for labelling. 3M Health Care submitted that not specifying the type of person be it male/female: volunteer/patient: young/elderly: mild/moderate/severe symptomatology: type of device used, press and breathe aerosol/breath actuated aerosol or dry powder device, did not materially affect the fact that there was a fundamental difference in deposition between Qvar and CFC-BDP. Such labelling did not mislead, add or detract from the simple message conveyed.

APPEAL BOARD RULING

The Appeal Board noted the data regarding the lung deposition values of CFC-BDP in a patient with asthma and considered that this supported the differences between CFC-BDP and Qvar seen in the volunteer studies. The Appeal Board considered that given that deposition data in patients with mild to moderate asthma was comparable to that in healthy volunteers it was not unacceptable to present healthy volunteer data and the failure to label the scintigram did not render the piece misleading. No breach of the Code was ruled with regard to the product summary and the patient information leaflet.

The appeal was successful.

2 Inaccurate claims regarding safety

On page 2 of the 'Dear Doctor' letter was the claim 'In fact Qvar, even at the maximum daily dosage of 800mcg, has no clinically significant effect on measures of adrenal function'. [In its complaint Glaxo Wellcome omitted the word 'clinically'].

Page 10 of the product summary was headed 'Does Qvar improve the therapeutic ratio of BDP?'. In a section of the page headed 'No clinically significant effects on adrenal function' was a graph which showed the mean change from baseline in 24 hour urinary free cortisol values after 14 days' treatment.

On page 13 of the detail aid in a section headed 'No clinically significant effects on HPA axis' was the same graph as on page 10 of the product summary with the exception that standard error bars had not been included.

Slide 57 of the slide pack bore the claim 'Up to the maximum recommended dose (800mcg/day) 24-h UFC remained in the normal range' and slide 60 stated that 'Within the recommended dose range there was no evidence of clinically significant HPA-axis suppression with Qvar'.

COMPLAINT

Glaxo Wellcome alleged that the materials suggested that 800mcg CFC-free BDP had no significant effect on adrenal suppression and therefore that no patients receiving CFC-free BDP would experience problems with regard to systemic safety. Hypothalmic-pituitary-adrenal (HPA) function during corticosteroid therapy varied greatly from person to person, and it could not be predicted which patients or how many patients might become HPA-deficient as a result of the corticosteroid therapy they received.

Statements of this type were directly misleading as they suggested that no patient would have any clinically significant adrenal dysfunction while on CFC-free BDP. Other markers of systemic activity such as osteocalcin levels had been shown to be suppressed at doses as low as 400mcg/day CFC-BDP (Teelucksingh *et al* (1991)).

Where there was graphical representation (in the product summary and the detail aid) mean changes in 24 hour urinary free cortisols were presented as blocks, which visually implied that all patients lay within these blocks. The data presented on which this claim was based reported on 24 hour urinary free cortisol. The data showed that minimum values for HFA-BDP 400mcg and 800mcg were around minus 70% change from baseline. Thus neither CFC-free BDP nor CFC-BDP at 800mcg could be dismissed as having 'no clinically significant effects on adrenal function'.

Statements regarding 'no clinically significant side-effects' were inappropriate, more especially in view of the recent Medicines Control Agency (MCA) guidelines concerning promotional material on inhaled steroids. They also contradicted statements made in the Qvar SPC, section 4.4.

Glaxo Wellcome alleged a breach of Clause 7.7.

RESPONSE

3M Health Care stated that the systemic safety profile of Qvar might be a concern for the healthcare

professional because of the high lung deposition with the product. As the lungs provided a very efficient absorptive surface one might quite reasonably expect that greater systemic exposure (and possible adverse effects) might potentially occur when using Qvar compared with CFC-BDP inhalers because of the significantly improved lung delivery. It was important that the healthcare professional understood that there had been a full and accurate investigation to highlight any effects that the reformulation might have upon the safety profile of BDP.

The statements made regarding safety were based on well powered clinical trials that reflected current available evidence and which were supported by the clinical experience with Qvar. Data from these trials were provided in all promotional materials as adrenal responses to inhaled steroids were the most easily measured and clinically relevant safety parameters.

3M Health Care noted that the safety statements made on page 2 of the 'Dear Doctor' letter had once again been misquoted by Glaxo Wellcome which had omitted the word 'clinically'. The statement actually read: 'In fact Qvar, even at the maximum daily dosage of 800mcg, has no clinically significant effect on measures of adrenal function.'

It was generally accepted that CFC-BDP at doses of 800mcg per day had no clinically significant adverse effects in adults including adrenal or HPA effects. This was supported by several recent reviews:

> Thompson *et al* (1998) stated that 'The 800mcg day dose of CFC-BDP used as the comparator is generally regarded as having non-significant clinical effects in adult patients'.
>
> Grossman (1998) stated that '…in very broad terms, significant and clinically important adverse effects are unlikely to occur at doses of the conventional inhaled corticosteroids below 1000mcg per day. This applies to BDP, budesonide and fluticasone.'
>
> Lipworth (1993) stated that 'In general, HPA-axis suppression is extremely unlikely with doses of BDP or budesonide below 800mcg per day in either adults or children.'
>
> Barnes and Pedersen (1993) stated that 'Systemic side-effects [of glucocorticosteroids] are usually observed only when daily doses of >800mcg are inhaled…'.

The clinical data showed 800mcg Qvar to have similar effects on 24 hour UFC excretion compared with CFC-BDP at 800mcg per day and that these effects were significantly different to placebo. Standard error bars were included on the graph (in the product summary) to indicate variability around the mean data. The actual values for patients in this study were all within the normal range at the end of treatment. Plasma cortisol data in a large cohort of patients (n=466) showed similar results.

3M Health Care noted that Teelucksingh *et al* (1991), cited in the complaint by Glaxo Wellcome, was a letter describing a study in 16 healthy adult volunteers evaluating the systemic effects of up to 2000mcg CFC-BDP via a metered dose inhaler for a period of 10 days. The parameter assessed was plasma osteocalcin. A significant fall versus placebo was seen at doses above 400mcg per day; however the authors concluded that the clinical relevance of these findings should be established. This observation of the effect of low doses of BDP upon osteocalcin in a larger patient group over a longer dosing period did not appear to have been clarified to date in studies of more robust design.

The safety profile of Qvar was covered extensively in the SPC. Section 4.4 clearly stated that within the recommended dose range of 100-800mcg per day, the effects upon the adrenal system were within the normal range and warned against high doses for prolonged periods. Generally, high doses were considered to be above the maximum dose limit of 800mcg per day. Section 5.2 endorsed a wider safety margin for Qvar: 'At a daily dose of 800 micrograms, suppression of urinary free cortisol was comparable with that observed with the same daily dose of CFC-containing beclomethasone dipropionate, indicating a wider safety margin, as Qvar is administered at lower doses than the CFC product.'

3M Health Care stated that inhaled steroids were preferred to oral steroids precisely because they maximised the beneficial effects of corticosteroids whilst minimising the adverse systemic effects. A further comment was made in the SPC regarding the reduced risk of systemic effects with inhaled compared with oral steroids, in line with the recent advice issued by the MCA about oral and inhaled corticosteroids.

3M Health Care stated that its coments above applied equally to concerns raised about the detail aid and slides 57 and 60 in the slide pack.

PANEL RULING

The Panel noted Section 4.4 of the SPC headed 'Special warnings and special precautions for use' stated that BDP '…and its metabolites may exert detectable supression of adrenal function. Within the dose range 100-800 micrograms daily, clinical studies with Qvar have demonstrated mean values for adrenal function and responsiveness within the normal range. However, systemic effects of inhaled corticosteroids may occur, particularly at high doses prescribed for prolonged periods'.

The Panel noted that data provided by 3M Health Care referred to adverse events with up to 800mcg Qvar a day being 'unlikely to occur' and being 'generally regarded as having non significant clinical effects.'

The Panel also noted that the MCA had issued guidance on corticosteroids in the May 1998 issue of Current Problems on Pharmacovigilance.

The Panel noted that the materials cited by Glaxo Wellcome gave the impression that adrenal suppression was not a problem with Qvar. In the Panel's view this was not consistent with the SPC which referred to the possibility of BDP exerting detectable suppression of adrenal function and that systemic effects may occur. The Panel considered that the claims were misleading and did not reflect the

available evidence. A breach of Clause 7.7 of the Code was ruled. This ruling applied to all the material cited by Glaxo Wellcome in the complaint.

3 Inaccurate claims regarding side-effects

Page 10 of the product summary bore the claim 'In particular, inhalation-route problems like hoarse voice and cough were lower with Qvar (8% vs 12%; p<0.042)' beneath a bar chart which showed the percentage of patients with at least one treatment related adverse event in those patients taking placebo (10), Qvar (11) and CFC-BDP (16).

Page 2 of the 'Dear Doctor' letter stated '…Qvar has a lower incidence of local side effects such as hoarseness and cough compared to CFC-BDP'.

Page 12 of the detail aid in a section headed 'Low overall incidence of side effects' [in its complaint Glaxo Wellcome omitted the word 'overall'] stated 'Summary of safety data from five studies including measurements of dysphonia, cough and worsening asthma symptoms'. This was followed by the same bar chart as in the product summary.

COMPLAINT

Glaxo Wellcome stated that it was claimed that side effects such as dysphonia (hoarse voice) and cough were lower with CFC-free BDP than with CFC-BDP. The bar chart in the product summary referred to patients with at least one treatment related adverse event and showed statistically significant differences between Qvar and CFC-BDP (p=0.012).

The study referenced (Thompson *et al* (1998)) showed no difference between the two treatments in respect of hoarseness and cough. The incidence of dysphonia was 3% in both groups, while the incidence of cough was <1% for CFC-free BDP (n=5) and 2% for CFC-BDP (n=6).

Glaxo Wellcome alleged that the material was in breach of Clause 7.2 as it was misleading and did not reflect the evidence.

RESPONSE

3M Health Care stated that the product summary discussed the adverse event profile of Qvar.

The bar chart showed the overall incidence of treatment related adverse events. There were significantly fewer reports in the Qvar group (11%) compared with the CFC-BDP group (16%) p=0.012. These adverse events could be further sub-divided into body system. When inhalation-route problems were examined again statistically fewer reports were seen in the Qvar group (8%) compared with the CFC-BDP group (12%) p<0.042 and this was commented upon underneath the graph.

The majority of the intended audience was unlikely to be familiar with the body system classification of inhalation-route disorders. The addition of 'like hoarse voice and cough' was included to enlighten the reader as to the context of the data and not to indicate values from specific sub-sections within the classification. This statement clearly reflected the Thompson study used to support this element. The author stated that 'The incidence of inhalation-route adverse events, whether related to corticosteroid presence or to propellant and excipients (e.g. dysphonia, cough, asthma symptoms) was lower with CFC-free BDP (8%) than with CFC-BDP (12%); p=0.042)'.

3M Health Care stated that the graph made it quite clear that the relative frequencies quoted compared the inhalation-route problems overall, which were statistically significantly lower for Qvar (8%) compared with CFC-BDP (12%). The phraseology used was intended to clarify not directly mislead or misrepresent the data and appeared to have been misinterpreted by the complainant.

A further breakdown of the figures was provided in the table appearing in Thompson's review which was presented in other promotional materials, eg slide 56 of the slide pack.

Again Glaxo Wellcome had misquoted the statement above the bar chart in the detail aid by omitting the word overall in the complaint. The header actually read: 'Low overall incidence of side-effects'. This claim was supported by the Thompson review. The comments above regarding the product summary applied equally to this bar chart and once more 3M Health Care considered that this had been misinterpreted by the complainant.

PANEL RULING

The Panel examined the Thompson paper which included adverse event data from five Phase III clinical trials involving 1429 patients in total. The overall incidence of adverse events was lower for Qvar (11%) than for CFC-BDP (16%) p = 0.012. The incidence of inhalation-route adverse events was also lower for Qvar (8%) than CFC- BDP (12%) p = 0.042. The inhalation-route disorders were listed as cough, dysphonia, increased asthma symptoms, site sensation and taste sensation. The incidence for each was given in the paper. None were statistically significantly different apart from the incidence of increased asthma symptoms (Qvar <1% vs CFC-BDP 1% p = 0.02).

The Panel considered that the claim 'In particular, inhalation-route problems like hoarse voice and cough were lower with Qvar (8% vs 12%; p <0.042)' suggested that there was a difference in the incidence of hoarse voice and cough for Qvar compared to CFC-BDP and this was not so. The Panel considered that the claim was misleading and did not accurately reflect the evidence. A breach of Clause 7.7 of the Code was ruled. The Panel considered that this ruling applied to all the materials cited by Glaxo Wellcome.

APPEAL BY 3M HEALTH CARE

3M Health Care accepted the Panel's ruling on the product summary and 'Dear Doctor' letter and undertook to modify the former with immediate effect. No further copies would be issued contrary to the ruling.

However, in the detail aid the stab line referred to overall side effects, not local side effects. In this detail

aid the data presented were accurate, correctly referenced, and 3M Health Care did not consider the presentation to be misleading. The crucial difference being the use of the word 'low' and not 'lower' as in the two items that it was not appealing. At no stage in the detail aid did 3M Health Care make any claims for differences in incidence of dysphonia or cough, nor did it highlight the symptoms. Thus 3M Health Care appealed the Panel's ruling for the detail aid that the presentation was misleading.

APPEAL BOARD RULING

The Appeal Board accepted that the claim in the detail aid 'Low overall incidence of side effects' in relation to a 'Summary of safety data from five studies including measurements of dysphonia, cough and worsening asthma symptoms' was a statement of fact. It was not comparative like the claims in the 'Dear Doctor' letter and the product summary. The Appeal Board accepted the submission from 3M Health Care and ruled no breach of the Code with regard to the detail aid.

The appeal was successful.

4 Disparaging the products of other companies

Page 3 of the product summary stated '…we have accepted relatively inefficient delivery systems with little or no question…'.

COMPLAINT

Glaxo Wellcome stated that this was neither accurate nor a fair reflection of the situation. As a result of extensive research by pharmaceutical companies, breath-actuated metered dose inhalers, large volume spacers and dry powder inhalers had been introduced specifically and successfully to address the issue of drug delivery. The statement disparaged the delivery devices of other pharmaceutical companies. A breach of Clause 8.1 was alleged.

RESPONSE

3M Health Care pointed out that the statement '…we have accepted relatively inefficient delivery systems with little or no question…' had been taken out of context, the full statement read: 'However, our very dependence on aerosol drug delivery to the lung for managing asthma symptoms has meant that we have accepted relatively inefficient delivery systems with little or no question provided that an acceptable clinical response was observed.'

3M Health Care considered that this accurately and fairly reflected the comments made by Howarth (1998) in the reference used to support this statement: 'Inefficient drug delivery systems for inhalation therapy have been accepted pragmatically in the management of asthma, as long as they deliver a sufficient dose to achieve a clinical response.'

It could be argued that an 'ideal' inhalation delivery system would deliver 100% of the dose to the target organ, with no wastage to non-target sites in the patient, nor hold-up in the delivery device itself. There were many factors which affected delivery of drug to lung from an inhaler device, some of which were device-design related, some of which were related to patient factors eg inhaler technique, inspiratory flow rate etc.

With new data supporting the improved efficiency of delivery of Qvar and the considerable *in vitro/in vivo* deposition data available for CFC-metered dose inhalers (MDIs) and dry powder inhalers (DPIs), 3M Health Care knew that even without considering patient reliant factors (eg inspiratory flow rate, co-ordination/inhaler technique), lung delivery of the emitted dose could be variable, ranging from 11.2% (for an MDI) to 20.8% (for a 3M breath-actuated MDI). Indeed, radio-labelling of CFC-BDP by Leach in healthy volunteers demonstrated a deposition range of 3% to 6%, with a mean of 4%. Recent work by Warren et al investigated radio-labelled CFC-BDP and a novel BDP dry powder inhaler in terms of lung deposition in healthy volunteers. The lung deposition for the CFC-BDP was 7.6% which would seem to agree with Leach's data.

The introduction of inhaler devices which were breath-actuated and the use of MDI/spacer combinations could improve drug deposition in the lungs but primarily as a result of improving the patient's inhaler technique. Such devices did not generally alter the respirable particle size distribution (and hence the consequent lung deposition) in the way that the Qvar reformulation had been shown to do.

In comparison with Qvar (values of >50% lung deposition data from both patient and volunteer studies, using either an MDI or the breath-actuated Autohaler device), the inhaler devices routinely used to date could be considered to be relatively inefficient delivery devices. The statement was not meant to disparage any particular inhaler product or manufacturer, but to indicate that opportunities for improving delivery efficiency did exist, and these had been realised to a considerable extent by 3M Health Care in the formulation of CFC-free BDP.

PANEL RULING

The Panel noted the submission from 3M Health Care regarding lung deposition data for the various products and devices. The Panel noted the context of the statement and did not accept that it was disparaging to refer to accepting relatively inefficient delivery systems with little or no question provided that an acceptable clinical response was observed. The Panel ruled no breach of Clause 8.1 of the Code.

5 Inappropriate claims in material for patients

The front cover of the patient information leaflet bore the statement 'Keeping you healthy in a healthier environment'.

Page three of the same leaflet, under the heading 'The facts about your CFC-free asthma preventer inhaler (Qvar)' stated 'With CFC-containing inhalers most of the medicine goes to the mouth and throat, and only a little goes to the lungs. With Qvar, most of the medicine goes to the lungs where the medicine works to reduce inflammation.'

COMPLAINT

Glaxo Wellcome stated that the unqualified statement on the front cover of the patient information leaflet suggested that CFC-free BDP would keep the patient healthy, but this could not be predicted for every patient. The company noted that information about medicines should not raise unfounded hopes of successful treatment.

Glaxo Wellcome stated that the information given on page three might raise concerns with members of the public about other (CFC-containing) inhalers they might be using.

Glaxo Wellcome alleged a breach of Clause 20.2.

RESPONSE

3M Health Care stated that as already outlined, the leaflet would only be used by the healthcare professional in discussions with the patient once the physician had made the decision to prescribe Qvar. As well as providing answers to common questions the patient might have, the primary objective was to highlight the changes to the dosing for Qvar as confusion about this could potentially have safety implications for the patient. This leaflet was prepared in conjunction with the chief executive and the medical adviser of the National Asthma & Respiratory Training Centre and the medical adviser of the National Asthma Campaign.

When any change was made to a patient's therapy it was important to ensure that their confidence in their medication was not undermined. The enforced changeover to CFC-free therapy would happen to all patients currently using CFC metered dose inhalers to treat their respiratory disease and it was necessary to ensure that they felt confident that the change would not have a negative effect on their asthma management.

The statement 'Keeping you healthy in a healthier environment' allowed the healthcare professional to set the scene for the mandatory change to CFC-free inhalers. In general it was likely that a patient could reasonably expect any medicine prescribed for them to benefit their particular condition. In this context 3M Health Care did not believe that the statement constituted an 'inappropriate claim' or raised unfounded hopes of successful treatment.

Furthermore, the statement also appeared in the patient advice leaflet recently issued by the Department of Health about the change to CFC-free inhalers. This leaflet was presented to the Royal Pharmaceutical Society of Great Britain. A Glaxo Wellcome employee, representing the International Pharmaceutical Aerosol Consortium (IPAC), was also present at this meeting. IPAC was formed by pharmaceutical manufacturers to collaborate and co-operate in the development of CFC-free technology. No comments had been raised by Glaxo Wellcome on this statement at any subsequent UK IPAC meetings (which were currently chaired by Glaxo Wellcome).

The statement 'The facts about your CFC-free asthma preventer inhaler' on page 3 of the Qvar leaflet was followed by the brand name of Qvar. This was important because the leaflet specifically related to Qvar and not to other CFC-free inhalers. The leaflet was designed to help the patient to understand why the dosage of Qvar was different to CFC-containing inhalers and to avoid any potential safety implications should the patient be confused about this aspect of their treatment.

The lung deposition scintigrams were included on page 3 to illustrate the different lung deposition profiles of Qvar and the CFC-BDP products the patient had used previously, the statement in question described these 'pictures' in words. No comment or inference was made as to the likely clinical efficacy implications that these differences might have. In a subsequent section of the leaflet (page 5), the patient was introduced to the concept of a reduced dose with Qvar. The leaflet quite clearly stated that: 'This means that you may experience the same control of your asthma symptoms with a smaller dose of beclomethasone dipropionate than with CFC-containing inhalers'.

3M Health Care submitted that it was important that the patient understood and accepted the idea of taking less steroid when using Qvar whilst still maintaining equivalent control of their asthma to the CFC-BDP inhalers which they had relied upon previously. In this context 3M Health Care did not believe that this statement was likely to raise concerns about, nor undermine the confidence patients already had in, their current CFC-containing asthma inhalers.

It had to be remembered that this leaflet was only an aid to the healthcare professional in the discussion of transition to Qvar (see comments above). Advice from other NHS sources, eg the NHS executive regarding CFC transition, was also available to the public via the Internet. The recently issued Health Service Circular on the phasing out of CFC containing MDIs outlined the importance of discussion and reassurance about dose changes with the patient when Qvar was prescribed.

PANEL RULING

The Panel noted the submission that the statement 'Keeping you healthy in a healthier environment' was similar to a statement used in a Department of Health leaflet which discussed in general changes to CFC-free aerosol inhalers. No actual products were mentioned in the Department of Health leaflet.

The Panel had some concerns about the statement 'Keeping you healthy in a healthier environment'. On balance, in the context of the brochure as a whole, the Panel did not consider that the statement would raise unfounded hopes of successful treatment as alleged. No breach of Clause 20.2 of the Code was ruled.

The Panel noted that on page three the section headed 'The facts about your CFC-free asthma preventer inhaler (Qvar)' gave details of the differences in lung deposition between CFC-containing inhalers and Qvar and included the scintigram. The Panel considered that the striking visual difference between the scintigram for the CFC-inhaler and that for Qvar would raise concern with members of the public

about the CFC inhalers they might have used or might still be using.

The Panel noted that subsequent text (page 5) explained the fact that with Qvar more of the medicine reached the lungs and so a lower dose of Qvar might be needed to get the same asthma control than with CFC containing inhalers. The Panel considered that the section 'The facts about your CFC-free asthma preventer inhaler (Qvar)' with its reference to the deposition of CFC inhalers was not a balanced presentation of the facts. It had not been explained in this section that, despite the fact that less medicine reached the lungs from CFC-inhalers, the dose for CFC-inhalers was set such that asthma was nonetheless controlled. The Panel ruled a breach of Clause 20.2 of the Code.

APPEAL BY 3M HEALTH CARE

In the patient leaflet the Panel ruled a breach due to the use of deposition visuals and omission of any confirmation that current CFC inhalers were effective.

3M Health Care did not agree with the Panel's ruling. It reiterated that this item was produced with full co-operation and review by both the medical adviser of the patients' representative body and by the primary asthma nurse training body in the UK. The information in the leaflet was constructed in response to real patients' actual questions and concerns developed from patient market research. 3M Health Care considered that altering the material, and the inclusion of unnecessary caveats, was a disservice to patients, and contrary to the clear communications they required (and had requested). In support of this case 3M Health Care supplied the opinion of the Director of the National Asthma and Respiratory Training Centre.

APPEAL BOARD RULING

The Appeal Board noted that the section headed 'The facts about your CFC-free asthma preventer inhaler (Qvar)' was followed by the scintigram which showed a striking visual difference between the CFC inhaler and Qvar. Beneath the scintigrams were figures of 4% for the CFC inhaler and 51% for Qvar. In the Appeal Board's view these figures emphasised the difference in the inhalers and might suggest to some readers that Qvar was twelve times better than CFC inhalers. The Appeal Board was concerned that the text beneath the scintigram did not explain that despite the fact that less medicine reached the lungs from CFC inhalers, the dose was set such that asthma was nonetheless controlled. The Appeal Board considered that some readers would get the impression that the reason they were being switched to Qvar was that CFC inhalers did not work. The Appeal Board considered that the section was not a balanced presentation of the facts and upheld the Panel's ruling of a breach of Clause 20.2 of the Code.

The appeal was unsuccessful.

Complaint received **5 November 1998**

Case completed **31 March 1999**

CASE AUTH/790/11/98 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v SMITHKLINE BEECHAM

Vaccine support services

A general practitioner complained about SmithKline Beecham's vaccine support services, submitting an advertisement which stated 'If you'd like to find out more about how we are putting service before sales, contact us on…'. The complainant had attended a travel health conference and been given a copy of a Vaccines Service Guide. The complainant had had difficulties making contact with his local representatives and subsequently only limited success in obtaining support items listed in the Service Guide, being told that he did not purchase sufficient quantities of vaccines to qualify. The complainant alleged that the arrangements regarding the provision of support services were such that they were an inducement to prescribe, supply, administer or buy a medicine in breach of the Code.

The Panel noted that SmithKline Beecham's version of events differed to that of the complainant. The complainant had stated that he had been told by the company's area manager that the provision of an anaphylaxis kit (which was subsequently provided) was linked to the volume of vaccines purchased. The area manager could not recall making such a remark. The Panel also noted that SmithKline had stated that its policy was clear, services would be provided to all who asked specifically for them. The services were not limited to sales. The policy had been reiterated to the whole salesforce.

The Panel accepted that extreme dissatisfaction was necessary on the part of an individual before he or she submitted a complaint. A judgement had to be made on the available evidence. The Panel was concerned about the inconsistencies between the parties' accounts but considered that it was not possible to determine where the truth lay and so no breach of the Code was ruled.

COMPLAINT

A general practitioner complained about the advertising by SmithKline Beecham Pharmaceuticals of its support services for the medical profession. The complainant provided a copy of an advertisement entitled 'Shut Up and Listen' (ref VA:AD/8/101U/GP), which stated, *inter alia*, 'If you'd like to find out more about how we are putting service before sales, contact us on…'.

The complainant stated that he was a single handed practitioner and therefore only bought vaccines in small quantities. Nevertheless he was constantly being offered various support services allied to vaccination, not only in advertisements like the one provided but also by SmithKline Beecham sales staff at various meetings. However, when he recently tried to avail the practice of some of these services he was told by his local representative that he did not purchase sufficient quantities to qualify. This was also reiterated by the area sales manager.

Clause 18 of the Code clearly stated 'The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine'.

Nowhere in any of SmithKline Beecham's literature was any mention made of minimum quantities of vaccines purchased in order to qualify for its support services.

The complainant alleged that SmithKline Beecham was in breach of the Code.

RESPONSE

SmithKline Beecham stated that there was a difference between service guarantees, which were provided to all customers centrally, and its support services, which required representatives' time to implement. The advertisement to which the complainant referred, 'Shut Up and Listen', was focussed solely on SmithKline Beecham's service guarantees, all of which applied to this general practitioner.

The services were outlined in the SmithKline Beecham Vaccines service guarantees and were offered and available to every customer. These service guarantees were recently updated. These guarantees covered the following subjects:

– speed of delivery
– confidence in refrigeration
– constant monitoring of supply
– regular updates
– instant access to all of the company's services
– flexible ordering
– clarity of invoices
– clarity of discounts
– ease of pack recognition
– advice on vaccine storage
– regular reviews of service quality
– service guarantee.

SmithKline Beecham stated that it had a policy for its service guarantees which clearly made no link between the provision of these services and the prescription, supply, administration or purchase of its vaccines. SmithKline Beecham would like further details of any incident considered in breach and would pursue it aggressively; without further information, it was difficult to pursue the complaint.

The issue that a representative and the area manager allegedly rejected the complainant's request on the grounds of insufficient vaccine sales was of grave concern to SmithKline Beecham and was not company policy. The company would be reviewing its internal procedures following this complaint.

SmithKline Beecham would be happy to discuss the service requirements with the complainant, at the complainant's convenience. It was also happy to reiterate the above to its sales staff as these points were fundamental to its customer service ethos.

In summary, however, and based on the available information, SmithKline Beecham did not believe it was in breach of Clause 18 of the Code.

* * * * *

Prior to making a ruling the Panel invited further comments from the complainant and from SmithKline Beecham.

FURTHER COMMENTS FROM THE COMPLAINANT

In response to a request from the Authority, the complainant provided further information and allowed his identity to be disclosed to SmithKline Beecham so that the company could look into the matter more closely.

The complainant stated that his complaint rested solely on the refusal of SmithKline Beecham to allow him access to its support services due to 'insufficient vaccines purchased', despite the fact that its promotional materials regarding its vaccine services had been freely given to him. It should be noted too, that the artwork on the SmithKline Beecham Vaccines Service Guide was the same as that in the advertisement and therefore should be seen as part of the same promotion.

The Service Guide at no point alluded to any condition attached to the support items – and neither should it, as this would be a clear breach of Clause 18.1 of the Code which stated:

> '…The provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer or buy any medicine…'

The complainant detailed the events that eventually led to his making the complaint:

6 May 1998 – travel health conference at a hospital. Long discussion with the representative manning the SmithKline Beecham promotional stand. Service Guide given to him. Written request for representative to visit him in his surgery.

Many telephone calls to customer services; requests via a SmithKline Beecham representative who visited him, but not on the vaccine side, were all to no avail. The complainant's area representative remained silent and invisible for many months.

27 August 1998 – Eventually, without the courtesy of making an appointment, the area representative arrived and was squeezed into a busy afternoon surgery. He stayed for 26 minutes – verified by the computer, discussed his products and promised support items to both the practice nurse and the complainant.

Nothing ever materialised, and eventually after further telephone calls to customer services, the complainant received a call from the representative and was told that he did not purchase sufficient

vaccines from SmithKline Beecham to be eligible for its support services.

This was then confirmed by the area manager who made no excuse for what he called 'the commercial world in which we live' and re-affirmed that the provision of support services was based solely on volume of vaccines purchased from SmithKline Beecham. The complainant thought that SmithKline Beecham had through the words and actions of its employees acted contrary to Clause 18.

FURTHER RESPONSE FROM SMITHKLINE BEECHAM

SmithKline Beecham stated that it had investigated the circumstances in this particular case and did not believe it had breached Clause 18.1 of the Code. The SmithKline Beecham Vaccine Services Guide detailed a number of services and products provided by SmithKline Beecham Vaccines. Most of these were related to quality of service for its products, which included vaccine specific initiatives, eg good speed of delivery, monitoring of supply, invoicing, pack recognition, etc. In addition, SmithKline Beecham also offered a number of other services, which included customer telephone team, distribution, medical information and a number of other offerings, eg patient education leaflets. All of these services were available to all customers.

SmithKline Beecham's medical director had written to the complainant and asked for an opportunity to discuss the issues raised (either in person or by telephone) in this complaint, but at the time of writing (27 January 1999) had not received a response. The complainant was a single handed general practitioner who attended a travel health conference and spoke to a representative at the SmithKline Beecham stand. He was apparently given a copy of the Vaccine Services Guide and at the same time requested that a representative visit. At this stage SmithKline Beecham could find no evidence that the complainant specifically requested service offerings.

The complainant did not receive a visit from the representative. Whilst this might have been sub-optimal from this customer's point of view, it was understandable given that targeting of customers occurred in line with business planning and this particular customer used no SmithKline Beecham vaccines. It was not clear to the SmithKline Beecham personnel involved, customer services and the SmithKline Beecham general medical representative, that the complainant was trying to obtain specific services.

Following a number of telephone calls, and in the interest of maintaining customer satisfaction, the area representative called on the surgery. He indeed arrived unannounced, gave his business card and asked whether it was a convenient time or should he return another day. He was asked to wait and after 20 minutes the complainant saw him. A detail of vaccine products followed. During the conversation the complainant specifically requested two service offerings, firstly a book (cost to SmithKline Beecham less than £5) and secondly an anaphylaxis pack. The book was given at this time and the representative noted that the anaphylaxis pack had already been given to the practice nurse. It was therefore the belief of SmithKline Beecham's representative that specific requests for service offerings had been met in line with company policy.

The practice manager then telephoned the representative complaining that the practice was being discriminated against on the basis of size. SmithKline Beecham was not aware of the reason for this feeling. As the practice was dissatisfied, the representative advised the practice manager to contact the area manager.

The area manager proactively called the practice and spoke to the complainant. The complainant told the area manager that the representative was too forceful and he was entitled to services and was being discriminated against as he had a small practice. The area manager apologised and said that he was surprised at the comments about the representative on whom he had received nothing but good feedback. The area manager stated that representatives' time was finite and that the complainant had received the specific services he had requested. He stated that clearly representative resource was prioritised to practices which gave the company business. A range of services were applicable which would suit different practices but this did not amount to discrimination. The area manager could not recall ever making the comments attributed to him. The conversation concluded amicably and he was thanked by the complainant.

SmithKline Beecham stated that it did not did not have unlimited representative resources and it made no apology for differential representatives' activity. The company believed that its team had at all times behaved professionally and in keeping with the Code. They had kept within company policy which was briefed to the fieldforce verbally and in writing at intervals. The area manager had passed the ABPI representatives examination with distinction as had the representative. SmithKline Beecham's policy was clear, services offered would be provided to all who asked specifically for them. These services were not linked to sales. This policy had been reiterated to the whole salesforce to ensure understanding.

In summary, SmithKline Beecham did not believe that it had breached Clause 18.1 of the Code. There were some differences of opinion about what was actually said and SmithKline Beecham would be happy to discuss this further with the complainant to answer any outstanding complaints.

SmithKline Beecham's further comments above were sent to the complainant for comment.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that he did receive a copy of a book during the meeting with the representative but the anaphylaxis kit had not already been provided directly to the practice nurse and to date had not been received.

Prior to the meeting with the area representative the complainant had requested both the book and the anaphylaxis kit. As the representative proved to be very elusive the practice manager spoke to a customer services team leader. He promised to dispatch the

anaphylaxis kit, a flip chart for interactive nurse/patient use and details of the computer information support to the practice immediately. They had never arrived.

The area manger refused to supply the practice with an anaphylaxis kit. The reason he gave was that the kit was tied in to the purchase of influenza vaccine from SmithKline Beecham.

The complainant noted that he had received the letter from SmithKline Beecham's medical director dated 21 January 1999 on 27 January 1999. It was therefore not surprising that SmithKline Beecham had not received a response to the medical director's letter by 27 January. On 4 February the practice manager spoke to SmithKline Beecham's medical director's secretary to arrange for the complainant to meet with the medical director on 24 February. This apparently being the first available time. The complainant stood by all his previous statements regarding specifically requested service offerings.

The complainant noted the submission by SmithKline Beecham that 'this particular customer uses no SmithKline Beecham vaccines'. The complainant pointed out that he had purchased vaccine to the value of £1,869.55 between 1 April and 31 December 1998. The complainant stated that the area manager did not call the practice. The representative provided the area manager's telephone number and suggested that the complainant contact him to confirm that 'service offerings were indeed linked to volume of purchase'. This was done. The complainant's recollection of the conversation he had with the area manager bore very little resemblance to his. Indeed it was the area manager's statement that the supply of an anaphylaxis kit was tied to the purchase of influenza vaccine that led him to make a complaint. The complainant noted that he was most precise in his documentation of events and ventured that had the area manager's recollection of the conversation been correct, there would have been no basis on which to make this complaint.

The complainant stated that there were many inconsistencies and untruths in SmithKline Beecham's letter and he was saddened that such a large organisation saw fit to 'bully' and discredit him.

The complainant stood by his original complaint that SmithKline Beecham had by the actions and words of its representatives, breached Clause 18.1.

PANEL RULING

The Panel noted that Clause 18.1 provided that no gift, benefit in kind or pecuniary advantage should be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer or buy any medicine. The supplementary information to Clause 18.1 provided an exemption in relation to the provision of medical and educational goods and services provided they were not an inducement to prescribe, supply, administer or buy any medicine. The supplementary information to Clause 18.1 – Package Deals – stated that Clause 18.1 did not prevent the purchaser of particular medicines receiving other associated benefits, such as apparatus for administration, provided that the transaction as a whole was fair and reasonable. In the Panel's view the benefits should be such that they related to the proper use of the medicine involved.

The Panel noted that SmithKline Beecham provided service guarantees and in addition other support services which it stated were available to all customers. The service guarantees and support services were set out in the SmithKline Beecham Vaccines Service Guide. Some of the support services mentioned in the Guide were provided via an interactive information retrieval and communication system, including an audit guide, a database providing immunisation and malaria advice and a travel clinics forum. Other support services featured included patient educational materials, clinical information support, customer education and training (including the book in question), a vaccines management pack, a mailing service, clinical support items and qualified agency nurse support. The SmithKline Beecham area manager had stated that a range of services was applicable which would suit different practitioners but this did not amount to discrimination. SmithKline Beecham had stated that all of the service guarantees and support services listed in the SmithKline Beecham Vaccine Service Guide were available to all customers.

The Panel observed that the parties' accounts differed. It was difficult in such cases to determine precisely what had transpired.

SmithKline Beecham had submitted that the complainant had specifically requested and received two support service items, namely a book and an anaphylaxis pack and had pointed out that the complainant was not a purchaser of SmithKline Beecham vaccines.

The complainant stated that he had requested a book, an anaphylaxis kit, a flip chart together with details of computer information support but had only received the book. The complainant stated that he had purchased £1,869.55 worth of SmithKline Beecham vaccines between April and December 1998.

The parties' accounts of conversations between the complainant and the representative and the complainant and the area manager also differed. The complainant recalled that the area manager and the representative linked the provision of the anaphylaxis kit to the volume of influenza vaccine purchased. The area manager at SmithKline Beecham could not recall making the statements attributed to him. In the Panel's view the provision of an anaphylaxis kit in association with the purchase of the vaccines could be an acceptable package deal.

The Panel accepted that extreme dissatisfaction was necessary on the part of an individual before he or she submitted a complaint. A judgement had to be made on the available evidence. The Panel was concerned about the inconsistencies between the parties' accounts but considered that it was not possible to determine where the truth lay. In these circumstances the Panel decided to rule no breach of Clause 18.1 of the Code.

Complaint received **4 November 1999**

Case completed **6 April 1999**

AURUM v MEDEVA PHARMA

Promotion of Minijet

Aurum complained about Medeva's use of the term 'pre-filled syringe' to describe its Minijet range of products. A pre-filled syringe, in Aurum's view, was a presentation that was ready to use and needed no assembly.

The Panel considered that 'ready to use' and 'pre-filled syringe' were different concepts and did not both necessarily apply in any particular situation. The term pre-filled syringe merely referred to the fact that there was no need to put the medicine in a syringe from an ampoule or similar before it could be used. The Minijet required the assembly of two components and thus could not be regarded as ready to use but the Panel considered that it did nevertheless involve a pre-filled syringe. No breach of the Code was ruled.

Upon appeal by Aurum, the Appeal Board noted that with the Minijet there was no need for an ampoule to be opened and a solution to be drawn up into a syringe barrel. The Appeal Board did not, therefore, consider the description of Minijet as a pre-filled syringe to be misleading and upheld the Panel's ruling of no breach of the Code.

Aurum Pharmaceuticals Limited complained about promotional material for Minijet used by Medeva Pharma Limited (formally Evans Medical) which described it as a 'pre-filled syringe'. (The Minijet system was manufactured by International Medication Systems (IMS) but marketed by Medeva).

COMPLAINT

Aurum stated that at a meeting held at a hospital, Medeva was using promotional material that described Minijet as a pre-filled syringe. This product was a multi component system which consisted of two main parts and needed assembly prior to use. It was clear to Aurum that the presentation was not a pre-filled syringe and should be described as a cartridge device or similar.

A pre-filled syringe, in Aurum's view, was a presentation that was ready to use and needed no assembly. The Minijet should never be described as a pre-filled syringe.

Aurum alleged that this description breached Clauses 7.2, 7.3 and 7.4 of the Code.

Aurum pointed out that in a previous case, AUTH/480/12/96, the Panel had ruled that the Minijet system was not a pre-filled syringe.

In its response to Aurum, the Authority pointed out that there had been no ruling in Case AUTH/480/12/96 regarding the Minijet as the case concerned Aurum's promotional material and not that of Evans Medical. The statement concerning the Minijet was an expression of opinion by the Appeal Board and not an actual ruling.

RESPONSE

Medeva did not consider the words 'pre-filled syringe' to be a product claim but part of the product description.

The essence of a pre-filled syringe was that the medicine was pre-loaded in a glass vial and could be used quickly in an emergency with minimal delay and with no mixing or loading of the medicine being required.

Medeva did not agree with Aurum's statement that a pre-filled syringe had to be ready to use and needed no assembly. Most pre-filled syringe systems required some action, be it assembly or preparation prior to use ie removal of a bung or needle guard or insertion of a plunger. There were several products that required insertion of a needle or even a needle change after mixing that had pre-filled syringe as their product description. 'Minijet pre-filled syringe' had been Medeva's trade mark in the UK since 1976 and was used globally to describe the product not only in promotional terms but also on packaging and medical information. Furthermore while using its trade mark Medeva never made a 'promotional' claim that its pre-filled syringe was ready to use.

Also, more importantly, current clinical practice accepted and understood the description Minijet pre-filled syringe and the term was used by the Resuscitation Council UK when discussing drug treatment. In the British Medical Journal, 3 May 1986, in an article entitled 'Advanced Life Support in General Practice' a member of the Council stated that 'some drugs are available in IMS pre-filled syringes.' The Pharmaceutical Journal, 18 February 1989, contained an article by another member of the Council which stated 'the system includes pre-filled syringes (Minijets).' To suggest a change would cause confusion amongst pharmacists and healthcare professionals.

Therefore Medeva did not accept Aurum's complaint. Medeva's products were well accepted, the product description Minijet pre-filled syringe was fully understood by healthcare professionals and they had been safely used in the UK for over 20 years.

Medeva supplied copies of a single page card (ref HZ19/2/50) listing products available in the Minijet range and stating on the front 'Minijet pre-filled syringe'.

PANEL RULING

The Panel noted that the Appeal Board's observation concerning the Minijet in Case AUTH/480/12/96 was in the context of an allegation about a claim of 'ready to use' in relation to the promotion of Aurum's product. It was not a ruling about the Minijet.

The Panel considered that two concepts were becoming confused, 'ready to use', as in the previous case, and 'pre-filled syringe', as referred to in both the previous and present cases. The two concepts did not both necessarily apply in any particular situation. For example, a product pack might contain a pre-filled syringe which did not have a needle already on but with a needle separately packed within the same outer package. The pack containing the syringe would have to be opened, the pack containing the needle would have to be opened, and the two would then be united to make the syringe ready for use. Such a presentation could perhaps not be described as 'ready to use' but could nonetheless correctly be described as involving a 'pre-filled syringe'. The term 'pre-filled syringe' merely referred to the fact that there was no need to put the medicine in a syringe from an ampoule or similar before it could be used. In the opinion of the Panel it was possible for a product pack to include a pre-filled syringe and yet not be ready to use.

Although the physical arrangements were different in the case of the Minijet, the Panel considered that same principle applied. The Minijet required the assembly of two components and thus could not be regarded as 'ready to use' but it did nevertheless involve a 'pre-filled syringe'. No breach of the Code was ruled.

APPEAL BY AURUM

1 In the previous case (Auth/480/12/96) the definition of 'ready-to-use' was discussed.

Taking the range of products namely prefilled syringe, cartridge system, ready-diluted vial + disposable syringe, and ampoule of concentrate + diluent + disposable syringe, Aurum stated that all of these products could be described as 'ready-to-use' with varying degrees of manipulation. Clearly, particularly in the therapeutic area of resuscitation products, this product-oriented definition was of no value. The definition should relate to the user, who would find the above list as more or less 'ready-to-use'. In resuscitation, the user would normally have an intravenous (IV) line in place, and therefore the product that was 'ready-to-use' was the one that could be attached to the line and the dosage given without prior manipulation. Only the Aurum pre-filled syringe met that definition. For this same reason, the term 'pre-filled syringe' did imply an advantage equivalent to the term 'ready to use', and therefore it should not be used where the product was not ready to use. It would be recalled that in the previous case, this argument was accepted.

2 Medeva maintained that it did not make a promotional claim that its system was a pre-filled syringe. Again Aurum referred to the prior case, where it pointed out that IMS portrayed the product in its assembled form in promotional literature, thereby implying that the product was ready to use. If this was not an issue, surely the company would portray the product in the form it was actually supplied. This amounted to use of the term, coupled to the illustration, in a promotional manner. It was moreover misleading and, in respect of emergency use, in breach of Clause 7.6 of the Code.

3 Reference to journals and manuals, which picked up on the description of pre-filled syringe used by IMS, was not evidence that it met any definition of such a device. If confusion was to arise by insisting that the IMS system was not a pre-filled syringe, it only arose because the prior use was strictly misleading.

4 In the 'Guidelines relating to the demarcation between: Dir. 90/385/EEC on implantable medical devices, Dir. 93/42/EEC on medical devices, and Dir. 65/65/EEC relating to medicinal products and related directives' (MCA EuroDirect Publication no EC2 (Rev.5.1), a distinction was made between a prefilled syringe, which was classed as a medicinal product, and a cartridge system, such as an insulin pen, where the cartridge was a medicinal product and the pen a device. In regulatory terms a disposable giving device such as used in the Minijet system normally meant that it was treated as part of the medicinal product. Functionally however, there was no distinction between the insulin pen and the Minijet system, dental cartridge systems, and the like. In other words, the Minijet system was a cartridge system, as was agreed in the previous case.

5 Another pharmaceutical company used the same Minijet system for its morphine product. Assembly instructions on the carton required the user to 'remove protective caps from the vial and injector before use, insert vial into injector, rotate vial three times in a clockwise direction until some resistance occurs, then rotate vial another half turn' (five separate actions which would not be needed with a true pre-filled syringe). Such a set of instructions did not comply with the term 'ready to use' which would only be applied to a pre-filled syringe such as supplied by Aurum. Equivalent instructions appeared on the resuscitation products supplied by IMS.

RESPONSE BY MEDEVA PHARMA

1 Case AUTH/480/12/96 had no bearing on the current complaint and Medeva was not able to comment fully on this case as it was not involved in the discussions. However the statement that Minijet was not a pre-filled syringe was totally wrong and was irrelevant to this complaint. Confusion was arising between the words pre-filled syringe and ready to use. Medeva did not make any claims to be ready to use and the term 'Minijet pre-filled syringe' was a trade mark that had been used and widely accepted in the UK for over 20 years. The term pre-filled related to the pharmaceutical product and was understood by pharmacists and clinicians and was used by the British National Formulary to describe Minijet syringes. Medeva gave examples of where the term was used by other manufacturers to describe their products.

2 Medeva's promotional literature did not imply that the product was ready to use, but illustrated the product in a form readily accepted by the end users. If Aurum's argument was extended, then companies would not be able to show a device such as an inhaler. They also had to be prepared to be ready to use. Clearly there was no breach of Clause 7.6.

3 Medeva did not refer to a journal 'pick up' of the term pre-filled syringe but to published guidelines of the Resuscitation Council of the UK in a peer reviewed reputable journal. A letter from a member of both the UK and European Resuscitation Committees was provided.

4 In the Guidelines relating to the Demarcation between: Directive 90/385/EEC on active implantable medical devices, Directive 93/42/EEC on medical devices and Directive 65/65/EEC relating to medicinal products and related directives (MEDDEV. 2. 1/3 Rev. 5.1 March 1998), the Commission stated:

6.2 'However if the device and the medicinal product form a single integral product which is intended exclusively for the use in the given combination and which is not reusable that single product is regulated as a medicinal product (article 1(3), second subparagraph MDD).'

There followed a list of nine examples of such products with 'Pre-filled syringes' listed first.

The components of Minijets did form a single integral product – the 'vial' acting as the syringe plunger. Minijets were single use, disposable products, and they were regulated in the UK as medicinal products.

To compare Minijets with insulin pens and dental cartridge systems was misleading, since both those cartridge systems were intended for repeated use and might be used with varying cartridge contents.

5 Neither the company which used the Minijet system for its morphine product nor Medeva made the claim 'ready to use'. Again Aurum's arguments were confused because the term pre-filled syringe referred to the pharmaceutical product not the state of the syringe. All these devices, as Medeva had stated before, required some prior manipulation before use.

Medeva repeated that the term Minijet pre-filled syringe was a well recognised descriptive trade mark that had been in use for over 20 years.

The letter from a member of both the UK and European Resuscitation Committees referred to by Medeva stated: "I write to confirm my description of your product Minijets as follows 'Minijets are convenient to use and act as a pre-filled syringe'".

FURTHER COMMENTS FROM AURUM

1 Aurum said that Medeva misled. The term 'Minijet prefilled syringe' was not a registered trade mark. Medeva had recently applied for such a trade mark, but Aurum's advice was that it was unlikely to be granted. The trade mark 'Min-i-jet' was registered as a Class 10 item for filled vials (no. 1041527). It was also registered under 'appliances for injection; surgical needles and syringes; medicament filled vials, ampoules and containers in cartridge form, all included in Class 10' (no. 1582379). Medeva's letter was therefore incorrect in this respect. Trade mark 1041527 was specific, and Aurum believed supported its contention entirely: these items were not pre-filled syringes. This was indeed a conclusion from Case AUTH/450/12/96, and Aurum could not see that this case had no bearing on the current case, as Aurum indeed specifically raised that as a basis for it. That Medeva was not present, in no way altered the considered opinion of the panel that judged the case.

2 Aurum believed it was important in resuscitation for products to be ready to use, which was the main market for the products under discussion. By showing the Minijet in its assembled form, Medeva implied that product was ready to use, which was a misrepresentation, and why Aurum suggested a breach of the Code. Aurum was not aware of any aerosol inhaler device which required four assembly and preparation steps before use, and so disputed the comparison made by Medeva.

3 While the Minijet might well have enjoyed a wide use in resuscitation in the past, there was no competitor to complain. The Authority presumably could not take action without a complaint, and practitioners in the field of resuscitation medicine would not have gained anything by raising a complaint, as then there was nothing truly ready to use available. Such an absence of a prior complaint did not invalidate one now.

4 When the Minijet was (finally) assembled, the 'giving set' was normally attached to the Venflon. It was routine and easier to remove the 'giving set' and dispose of it, but in theory one could insert the next Minijet vial into the previous 'giving set'. So practice dictated it fell under the category of a medicinal product for demarcation, but Aurum's point was still valid that it was closer to a cartridge system in design than a syringe (pre-filled or otherwise).

5 Aurum did not believe it was confused. Medeva would be well aware that the health services would pay a premium for resuscitation products as Minijets or Aurum's pre-filled syringes. The reason for this premium was solely in recognition of the need for a product which was quicker to use than ampoules or vials. If a member of the resuscitation team charged a disposable syringe with adrenaline and passed it to the doctor administering the medicine, then to that doctor the syringe was 'pre-filled'. If the doctor was passed a Minijet he had to assemble it first, or the assistant did that for him, what was analogous to pre-filling the syringe. Notably the correspondent stated in the copy letter enclosed that Minijets acted as a pre-filled syringe, presumably when he was passed it in the assembled form. Aurum's product mirrored the pre-filled syringe in this example, and had a distinct advantage over the Minijet.

Aurum believed that twenty years' practice without being corrected did not justify Medeva continuing these misrepresentations.

APPEAL BOARD RULING

The Appeal Board accepted that in Case AUTH/480/12/96 it was stated that 'In the Appeal Board's view, the Minijet system was not a pre-filled syringe'. However, the description of Minijet as a pre-filled syringe was not at issue in that case. The Appeal Board had not made a ruling and did not consider itself bound by a view which had been expressed in the course of considering another matter. This had been pointed out to Aurum.

The Minijet needed to be assembled before use; it was not a ready to use syringe. The Appeal Board noted, however, that with the Minijet there was no need for an ampoule to be opened and a solution to be drawn up into a syringe barrel. The Appeal Board did not, therefore, consider the description of Minijet as a pre-filled syringe to be misleading and upheld the Panel's ruling of no breach of the Code.

The appeal was unsuccessful.

Complaint received	**10 November 1998**
Case completed	**4 March 1999**

CASE AUTH/802/11/98 *NO BREACH OF THE CODE*

HEALTH AUTHORITY MEDICAL ADVISER v YAMANOUCHI PHARMA

Men's Health Matters – public awareness leaflet

A medical adviser to a health authority complained about a leaflet, funded by Yamanouchi Pharma and aimed at the general public, which gave the symptoms of prostate problems and encouraged readers who thought they might be so affected to contact their GP because, as the leaflet stated, 'Most prostate problems can be treated with medicines'. The complainant considered that, although no medicines were named, the leaflet was creating a potential demand for Yamanouchi's product, Flomax MR (tamsulosin), a prescription only medicine.

The Panel considered that the leaflet raised public awareness about prostate problems and the fact that they could be treated with medicines. Although the leaflet might facilitate the market development of Flomax MR, the Panel did not consider that the leaflet was an advertisement for the product to the general public. The leaflet might encourage patients to discuss prostate problems with their doctor but it did not encourage them to ask their doctor to prescribe a specific medicine. No breach of the Code was ruled.

A medical adviser to a health authority complained about a leaflet which had the title 'Male Over 50 Prostate Problems?'. The leaflet, in a series of questions to the reader, gave the symptoms of prostate problems and stated 'No it isn't 'your age', and something simple can be done about it. Most prostate problems can be treated with medicines. Your doctor will be able to help. Ring the surgery NOW to make an appointment'. A free information leaflet was offered through a freephone number. At the bottom of the leaflet was a logo, MHM, and 'Men's Health Matters'.

COMPLAINT

The complainant stated that a general practitioner had brought the leaflet to his attention. The general practitioner had said that the leaflets were being distributed within the community which he served. He had indicated his objection to the procedure and had established that the leaflets were funded by Yamanouchi Pharma Ltd.

The complainant had spoken to the medical director of this company indicating that the leaflet was causing concern within the general practitioner community in the area. Her response was that Men's Health Matters, though it might receive financial support from her company, was not within her control. She felt therefore that any complaint that might be made under the Code would be rejected.

The complainant's own feeling was that though the leaflet did not mention a specific medicine it was in effect creating a potential demand for a product of Yamanouchi. He believed therefore that it was potentially a breach of Clause 20 of the Code.

RESPONSE

Yamanouchi stated that Men's Health Matters was a health education unit set up by a healthcare communication company in 1995. Its aim was to create awareness concerning men's health and it received medical support from a panel of specialists.

In 1997 Yamanouchi initiated a health education programme concerning the prostate under the umbrella of Men's Health Matters. The leaflet had been seen and approved by Yamanouchi's medical director and director of marketing and the company was satisfied that the leaflet was not in breach of the Code and, specifically, not in breach of Clause 20, as it did not promote any product but merely provided information on a therapeutic area.

The distribution of the leaflets to the public was preceded by a letter to the general practitioners in the area, a copy of which was provided. Yamanouchi understood from the complainant that one GP had complained to the health authority that he/she knew nothing of this campaign. Yamanouchi regretted that the health authority would not allow it to investigate the case, before making a formal complaint. Having looked into the matter, Yamanouchi had found that in this case the letters to the GP's were not sent out prior to the public campaign. Yamanouchi had put into place procedures to ensure that no similar problems would occur in the future.

The reference to the conversation with Yamanouchi's medical director was not entirely accurate. The medical director stated that the distribution of the leaflet was not within her direct control, but that she would investigate the matter and apologised for any inconvenience. She also stated that there was no promotion of, or specific association with, any product, and she therefore did not feel that the leaflet was in breach of Clause 20 of the Code.

Yamanouchi did not believe that the leaflet even fell within the scope of the Code. Provision of information on a therapeutic area was not against the Code. Yamanouchi referred to Case AUTH/516/3/97 where the Appeal Board ruled no breach of Clause 20 in a similar case.

Yamanouchi supplied copies of the leaflet at issue and of the information leaflet, entitled 'Waterworks', which could be obtained through the freephone number. The letter to general practitioners was also provided.

Following a request for further information, Yamanouchi explained that it was currently the sole sponsor of Men's Health Matters which was an educational programme to educate men about their health. The campaign focussed on 'below the belt' issues including prostate disease. The programme was developed with an educational grant from Yamanouchi.

PANEL RULING

The Panel noted that the leaflet 'Male Over 50 Prostate Problems?' encouraged readers who had answered 'yes' to the series of questions about the symptoms of prostate problems, to go to see their doctor for help. The leaflet stated 'Most prostate problems can be treated with medicines'. No specific medicine or class of medicine was mentioned on the leaflet. There was no other reference to medicines in the leaflet. The Panel noted that Clause 20.1 of the Code stated that prescription only medicines (POMs) and certain pharmacy medicines must not be advertised to the general public. Yamanouchi had sponsored the leaflets in question and also marketed Flomax MR (tamsulosin) a POM for the treatment of benign prostatic hyperplasia. The Panel considered that the leaflet raised awareness about prostate problems and the fact that they could be treated with medicines. The leaflet might facilitate the market development of Flomax MR. The Panel did not consider that the leaflet was an advertisement for the product to the general public. No breach of Clause 20.1 was ruled.

The Panel noted the requirements of Clause 20.2 of the Code that information about medicines which was made available to the general public must 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 doctors to prescribe a specific medicine. The Panel accepted that the leaflet might encourage patients to discuss prostate problems with their doctor but the leaflet in question did not encourage patients to ask their doctor to prescribe a specific medicine. The Panel ruled no breach of Clause 20.2 of the Code.

During its consideration of this case the Panel noted that the leaflet made no mention of the fact that it had been sponsored by Yamanouchi. The Panel queried whether this was in accordance with Clause 9.9 of the Code, which required that all material relating to medicines and their uses which was sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company. The supplementary information stated that declaration of sponsorship must be sufficiently prominent to ensure that readers of sponsored material were aware of this at the outset. The Panel requested that its views be made known to Yamanouchi. In contrast the Panel noted that the Men's Health Matters information request line, accessible via the freephone number on the leaflet, stated in its introduction that 'This is a free service brought to you by Yamanouchi Pharma'. The 'Dear Doctor' letter sent to general practitioners gave details of Men's Health Matters and explained that it was a public awareness campaign for people with prostate problems. Yamanouchi's support for the project was clearly stated at the bottom of the letter.

The Panel noted that in its response to the complaint, Yamanouchi had provided a copy of the 'Waterworks' leaflet which could be obtained via the freephone number. The 'Waterworks' leaflet had not been complained about in this case. The Panel queried whether the 'Waterworks' leaflet was acceptable in relation to Clauses 20.1 and 20.2 of the Code. The Panel decided that this matter should be taken up with Yamanouchi under Paragraph 16 of the Constitution and Procedure but before this had been done a complaint was received which covered similar issues (Case AUTH/827/1/98) and so no action was necessary under Paragraph 16.

The Panel considered that its views regarding declaration of sponsorship of the leaflet supplied by the complainant also applied to the 'Waterworks' leaflet.

Complaint received **19 November 1998**

Case completed **9 February 1999**

CASE AUTH/805/11/98

LEO v CROOKES HEALTHCARE

Curatoderm detail aid

Leo complained about a detail aid for Curatoderm (tacalcitol) issued by Crookes Healthcare. The statements 'Combine with topical corticosteroid' and 'Combine topical vitamin D analogue with short-contact dithranol cream' appeared as stages in a flowchart headed 'Treatment protocol for guttate and plaque psoriasis'. Leo alleged that the claim that Curatoderm could be used in combination with topical corticosteroids and the claim that it could be used in combination with dithranol cream were inconsistent with the summary of product characteristics (SPC). Further, Leo alleged that Curatoderm was not indicated for the treatment of guttate psoriasis.

The Panel noted that Curatoderm was licensed for psoriasis vulgaris. The Panel considered that the treatment protocol promoted Curatoderm for the treatment of guttate psoriasis and this was inconsistent with the SPC. A breach of the Code was ruled.

The Panel noted that the Curatoderm SPC made no mention of the use of the product in combination with topical corticosteroids or dithranol cream. Such use was neither recommended nor prohibited. The SPC was silent on the point. Combination treatment with ultraviolet light was mentioned in the SPC. No data had been supplied by Crookes to support the use of Curatoderm in combination with either topical corticosteroids or dithranol cream. On balance the Panel decided that the reference to combination therapy was inconsistent with the SPC and a breach of the Code was ruled.

Leo Pharmaceuticals complained about a detail aid (ref ZZ02162) for Curatoderm (tacalcitol) issued by Crookes Healthcare Limited. Leo stated that it had been reassured in respect of the claim 'effective and safe in the long term management of psoriasis' and that this particular item would be withdrawn by Crookes Healthcare on the basis of the inappropriate use of the word safe. Leo was still concerned however that other claims might continue to be made. Leo was particularly concerned because the Medicines Control Agency had informed Leo that promotion of its product Dovonex (calcipotriol) concurrently in combination with other anti-psoriatic treatments was inconsistent with the Dovonex marketing authorization and Leo would expect this to similarly apply to Curatoderm.

COMPLAINT

The statements 'Combine with topical corticosteroid' and 'Combine topical vitamin D analogue with short-contact dithranol cream' appeared as stages in a flowchart headed 'Treatment protocol for guttate and plaque psoriasis'. Leo alleged that the claim that Curatoderm could be used in combination with topical corticosteroids was not consistent with its summary of product characteristics (SPC) and was therefore in breach of Clause 3.2. The same applied to the claim that Curatoderm could be used in combination with dithranol cream. Leo further alleged that Curatoderm was not indicated for the treatment of guttate psoriasis. The claim was not consistent with the SPC and again was in breach of Clause 3.2.

RESPONSE

Crookes Healthcare stated that the three phrases quoted, namely 'Treatment protocol for guttate and plaque psoriasis', 'Combine with topical corticosteroid' and 'Combine with …dithranol cream' all came from a treatment protocol written by Chu (Current Issues in Dermatology; 1997) which had been reproduced, with minor modifications, in the Curatoderm detail aid. The adaptations consisted of graphical changes to improve legibility without omission of any material. The adapted protocol had been used in this form before in a Curatoderm detail aid issued by the previous holders of the product licence.

The Chu paper referred to improvements in quality of life for patients with psoriasis using the vitamin D analogues, tacalcitol and calcipotriol, without mention of any specific product, and the treatment regimes described were those of the author. Crookes was of the opinion that, had it made changes to the protocol or its heading, it would have been in breach of Clause 7.6 of the Code.

Crookes noted that it did not state or imply in the detail aid that Curatoderm was registered for the treatment of guttate psoriasis, nor that it was approved for use in combination with topical corticosteroids or dithranol cream.

Crookes did not, therefore, believe that there had been a breach of Clause 3.2 in respect of these particular complaints. Crookes had, however, already withdrawn this piece from use because it was acknowledged that it contained a separate breach of the Code.

PANEL RULING

The Panel noted that as the treatment protocol appeared in promotional material Crookes was responsible for the content as far as the Code was concerned.

The Panel noted that Curatoderm was licensed for psoriasis vulgaris. The SPC made no mention of guttate psoriasis which, according to a medical dictionary, was seen primarily in children and young adults especially following streptococcal infections and characterized by the abrupt appearance of small droplike lesions over much of the skin surface. The Panel noted that Curatoderm was not recommended for use in children. The Panel considered that the treatment protocol promoted Curatoderm for the treatment of guttate psoriasis and this was

inconsistent with the SPC. A breach of Clause 3.2 of the Code was ruled.

The Panel noted that the Curatoderm SPC made no mention of the use of the product in combination with topical corticosteroids or dithranol cream. Such use was neither recommended nor prohibited. The SPC was silent on the point. Combination treatment with ultraviolet light was mentioned in the SPC.

No data had been supplied by Crookes to support the use of Curatoderm in combination with either topical corticosteroids or dithranol cream.

On balance the Panel decided that the reference to combination therapy was inconsistent with the SPC and a breach of Clause 3.2 of the Code was ruled.

Complaint received **30 November 1998**

Case completed **8 February 1999**

CASE AUTH/807/12/98

GLAXO WELLCOME v ASTRA

Advertisement for Oxis 12 Turbohaler

Glaxo Wellcome complained about an advertisement for Oxis 12 Turbohaler (eformoterol) which had appeared on the back cover of Archives of Disease in Childhood, alleging that this was in breach of the Code because it was promotion to paediatricians though Oxis 12 was not currently licensed in childhood.

The Panel noted that the summary of product characteristics stated that children up to the age of 12 years should not be treated with Oxis Turbohaler as insufficient experience was available. The Panel considered that, given the restrictions on the use of the product in children, placing the advertisement in a paediatric journal amounted to the advertising, by inference, of Oxis 12 Turbohaler for an unlicensed purpose. This had been accepted by Astra. A breach of the Code was ruled.

Glaxo Wellcome UK Limited complained about an advertisement for Oxis 12 Turbohaler (eformoterol) issued by Astra Pharmaceuticals Ltd which appeared on the back cover of Archives of Disease in Childhood, December 1998.

COMPLAINT

Glaxo Wellcome was very concerned about the appearance of the advertisement on the back cover of Archives of Disease in Childhood as Oxis 12 was not currently licensed in childhood. However, the appearance of this large advertisement in a paediatric journal was, Glaxo Wellcome believed, promotion to paediatricians in breach Clause 3.2 of the Code.

RESPONSE

Astra said that Oxis Turbohaler was licensed for use in adults and children aged 12 years and above for the relief of broncho-obstructive symptoms in asthmatics when adequate treatment with corticosteroids was not sufficient. The summary of product characteristics was provided.

Having investigated this matter, Astra confirmed that it was not appropriate for the Oxis 12 Turbohaler advertisement to appear in a paediatric journal. This should not have happened and Astra shared the concern that it did not comply with Clause 3.2 of the Code. Immediate action had been taken to ensure that no further Oxis 12 Turbohaler advertisements appeared in Archives of Disease in Childhood after December 1998.

PANEL RULING

The Panel noted that the prescribing information in the advertisement referred to the dose in adults and stated that there was no clinical experience in children. The advertisement featured a photograph of a man leaning up against a tree in the midst of a tropical storm. There were no photographs of, and, apart from in the prescribing information, no references to children. The summary of product characteristics stated that children up to the age of 12 years should not be treated with Oxis Turbohaler as insufficient experience was available. The Panel considered that, given the restrictions on the use of the product in children, placing the advertisement in a paediatric journal amounted to the advertising, by inference, of Oxis 12 Turbohaler for an unlicensed purpose. This had been accepted by Astra. A breach of Clause 3.2 of the Code was ruled.

Complaint received **3 December 1998**

Case completed **7 January 1999**

CASE AUTH/810/12/98

HEALTH AUTHORITY ADVISERS v LILLY

Promotion of Evista

Three health authority advisers submitted a joint complaint about the promotion of Evista (raloxifene) by Lilly. Two journal advertisements claimed that 'Evista has reduced the incidence of newly diagnosed breast cancer in clinical trials' but the prescribing information stated that 'The long-term effect of Evista on the risk of breast cancer is unknown'. The complainants noted that Evista was not licensed for the prevention of cancer. It was alleged that the claim was ambiguous and misleading.

The Panel considered that the claim in question, 'Evista has reduced the incidence of newly diagnosed breast cancer in clinical trials' gave the impression that women on Evista would be less likely to develop breast cancer. Although the claim was derived from a statement in the summary of product characteristics (SPC) the Panel noted that the SPC, and the prescribing information, stated that Evista was intended for long-term use and that the long-term effect of the product on the risk of breast cancer was not known. The claim thus did not reflect all of the data with regard to the effect of Evista on breast tissue and the Panel considered that it was therefore misleading. It was immaterial that the additional data was included in the prescribing information as it was an accepted principle under the Code that misleading claims could not be qualified by the small print. A breach of the Code was ruled.

Upon appeal by Lilly, the Appeal Board noted that the two advertisements had a theme of 'protection'. Each was headed 'Non-hormonal protection for post-menopausal women' and a strapline at the bottom of the advertisements read 'Non-hormonal protection'. Between the heading and the strapline appeared three claims of equal prominence about Evista. The first claim 'Evista prevents bone loss and reduces the risk of vertebral fracture' clearly related to the licensed indication for the product. The third claim, 'Evista has reduced the incidence of newly diagnosed breast cancer in clinical trials', would, in the Appeal Board's view, also be seen as a licensed indication and another aspect of Evista's 'protection' for postmenopausal women. In addition the Appeal Board considered that the claim had not been put into context. It had not been clearly stated that the long-term effect of Evista on the risk of breast cancer was unknown. The Appeal Board considered that the context of the claim at issue and its position within the advertisements meant that the advertisements were misleading with regard to the effect of the product on the incidence of breast cancer. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Three health authority advisers submitted a joint complaint about the promotion of Evista (raloxifene) by Eli Lilly and Company Limited. In particular the complainants were concerned about a full page advertisement (ref EV 100 Aug 98) which had appeared on the outer back cover of the classified section of the BMJ, 14 November 1998. The advertisement featured the heading 'Non-hormonal protection for post-menopausal women' beneath which appeared three product claims. The third claim stated that 'Evista has reduced the incidence of newly diagnosed breast cancer in clinical trials'. The advertisement referred readers to the prescribing information which appeared on the right hand column of the inside back cover.

Enclosed with the complaint was a copy of an advertisement for Evista which had appeared as a double page spread in GP in November. This bore the same reference number, EV 100 Aug 98, but its layout was completely different, most notably in that the prescribing information ran along the bottom of the advertisement and so was not on a separate page to the promotional claims, and not all of the allegations were relevant to it.

COMPLAINT

The complainants stated that they were concerned about misleading claims made by Lilly for Evista. Although the full page advertisement in the BMJ claimed that Evista 'reduced the incidence of newly diagnosed breast cancer in clinical trials', the prescribing information on the previous page stated 'The long-term effect of Evista on the risk of breast cancer is unknown.' The prescribing information also noted a 53% reduction in the relative risk for newly diagnosed breast cancer in the Evista group compared to women on placebo. Was this, in the context of Clause 7.2 of the Code 'unambiguous'? Did this two sided advertisement meet the requirement that each side must not be misleading in isolation (Clause 6.2)?

A request to Lilly for further information on these points had been met promptly. The complainants considered, however, that in terms of today's standards of critical appraisal, the information on the design and conduct of the trials was inadequate and there was no explanation of the methodology for pooling results. There had been notable advances in both the use of metaanalysis, and its pitfalls. It seemed wrong to advertise a product on the basis of benefits for which there were no published clinical trials. Supplying abstracts and selectively reporting on trials fell short of the information the complainants needed to make decisions.

The conclusions of the complainants based on the information available to them were:

a) It was not possible to assess the quality of clinical trials where effects on breast cancer were assessed as secondary end-points. Therefore it was not possible to judge the potential for bias or confounding as possible causes of the relative risk reduction.

b) The long-term effects of Evista on breast cancer incidence were not known.

c) Evista was not licensed for the prevention of breast cancer.

If the results for the secondary end-point of newly diagnosed breast cancer were borne out by robust

clinical trials, the reduction of the incidence of breast cancer could be of enormous benefit.

Given the state and availability of knowledge available at present, the complainants found the advertisement ambiguous and misleading, particularly so to the general practitioner and general public.

RESPONSE

Lilly stated that it referred to 'newly diagnosed breast cancer in clinical trials' specifically to avoid ambiguity because this was similar to the wording that appeared in the summary of product characteristics (SPC) which was accepted by the European Medicines Evaluation Agency (EMEA) and described the results of the clinical trials and made no inferences beyond that. The statement 'the long term effect of Evista on the risk of breast cancer is unknown' was lifted directly from the SPC. The advertisement noted a 53% reduction in the relative risk for newly diagnosed breast cancer in the Evista group compared with women on placebo; the SPC stated that 'In clinical trials with Evista involving over 12,000 patients, most of whom have been exposed to at least 30 months therapy, the relative risk of newly diagnosed breast cancer was significantly lower (53% reduction, relative risk 0.47, CI 0.28, 0.78) in Evista – treated than in placebo-treated postmenopausal women'.

Some of these quotes were lifted not from the main body of the advertisement but from the prescribing information and in this context and with the quotations given by the complainants Lilly considered that these statements were accurate, balanced, fair, objective and unambiguous in line with Clause 7.2 of the Code – indeed because of the emotive nature of breast cancer Lilly had been very careful to stick to the accepted wording in the SPC in order to avoid ambiguity.

The complainants also asked if the two sided advertisement met the requirements of Clause 6.2 of the Code in that 'each side must not be misleading in isolation'. Lilly did not consider that the first page was misleading in isolation as it presented information that was contained in the SPC and in the prescribing information. There was clear reference to the prescribing information appearing overleaf.

Lilly was pleased to see that its medical information department had provided information promptly on request and thanked the complainants for pointing that out. Without knowing what was requested it was difficult to defend what information was sent out. The complainants referred to the inadequacy of the information on the design and conduct of the trials in terms of 'today's standards of critical appraisal'. Lilly thoroughly supported this approach which was usually applied to published study reports not to information provided by medical information departments. However had the complainants specifically requested information on the design and conduct of Lilly's studies the company would have been happy to provide them; Lilly's clinical research physician for Evista was quite used to answering specific questions on Lilly's studies and describing their design. Likewise, if information had been requested on the 'methodology for pooling results' Lilly would have been more than happy to provide this (for Evista, pooled results for breast cancer were simply every breast cancer case from all of the company's Evista osteoporosis prevention and treatment studies); pooling the crude data in this way avoided the pitfalls and potential problems of metanalysis which was therefore not indicated in this situation.

Lilly was somewhat confused by the statement by the complainants that 'Supplying abstracts and selectively reporting on trials falls short of the information we need to make decisions'. Lilly did not selectively report on trials, indeed in order to obtain a licence from the EMEA (or the FDA) full trial reports were provided. Lilly agreed that publication in peer reviewed journals was the ideal and most of Lilly's trials would be submitted in this way. The results of a two year interim analysis of the European osteoporosis prevention study were published in the New England Journal of Medicine, the results of other prevention studies and the osteoporosis treatment study had been submitted to international congresses from which abstracts had been published. This was the fastest way of getting important scientific information into the public domain. The aim was to publish as much of these data as was possible in peer reviewed journals.

The complainants had stated their conclusions based on the available information. Lilly commented on these in turn.

a) Lilly did not understand why the complainants stated that 'It is not possible to assess the quality of clinical trials where effects on breast cancer were assessed as secondary end-points'. The quality of any clinical study depended on its design and conduct; all of the trials from which these data were derived were randomised, double-blind, placebo controlled studies performed under International Conference on Harmonisation, Guidelines for Good Clinical Practice – the most scientifically rigorous trial methodology.

b) The long-term effects of Evista on breast cancer incidence were not known – that was what was stated in the SPC and Lilly agreed with this and made no other claims.

c) 'Evista is not licensed for the prevention of breast cancer' – this was exactly why Lilly stuck so closely to the wording in the SPC which described one of the pharmacological properties.

d) Lilly was grateful to the complainants for correctly pointing out that if these results for the secondary end-point of newly diagnosed breast cancer were borne out by robust clinical trials, the reduction in the incidence of breast cancer could be of enormous benefit: all of the trials from which these data were derived were randomised, double-blind, placebo controlled studies as discussed above; Lilly considered that there were few more robust trials.

Finally, the complainants repeated their concerns that the advertisement was ambiguous and misleading to the general practitioner and general public. Lilly did not promote any licensed medicines directly to the public and as the claims in the advertisement were related directly to the SPC or prescribing information and could be substantiated by clinical data (as required by Clause 7.3), Lilly considered that the advertisement was not misleading and was unambiguous.

PANEL RULING

The Panel noted that there was some confusion about the advertisement at issue. The complainants had provided a copy of a double page advertisement (ref EV 100 Aug 98) that had appeared in GP in November 1998. The letter of complaint referred to an advertisement (ref EV 100 Aug 98) that had appeared on two consecutive pages in the classified section of the BMJ (14 November 1998). Lilly had submitted that the advertisements would have been similar. The Panel noted that the advertisements may have been similar in content but they were very different in layout. In the Panel's view they were two different advertisements. The Panel noted that the guidelines on company procedures relating to the Code (page 37 of the Code of Practice booklet) stated that different sizes and layouts of a piece of promotional material should be separately certified and each should have its own unique reference number. The Panel requested that Lilly's attention be drawn to the guidelines.

The Panel noted that the Evista prescribing information stated that the product was for the prevention of non-traumatic vertebral fractures in postmenopausal women at increased risk of osteoporosis and that, due to the nature of the disease process, Evista was intended for long-term use. In a section headed Pharmacodynamics (effects on breast tissue) the prescribing information stated 'In clinical trials with Evista involving over 12,000 patients, most of whom had been exposed to at least 30 months' therapy, the relative risk of newly diagnosed breast cancer was significantly lower (53% reduction, relative risk 0.47) in Evista-treated than in placebo-treated postmenopausal women. The long-term effect of Evista on the risk of breast cancer is unknown'. The SPC was similarly worded.

The Panel noted that the complainants had criticised the information on the design and conduct of the trials, and stated that it was wrong to advertise products for which there were no published clinical trials. The Panel noted that the SPC referred to the data which had been accepted by the EMEA. The product had a marketing authorization which would have been granted on the basis of quality, safety and efficacy. It was not wrong to advertise products on the basis of unpublished data. Advertisements had to comply with the Code which required in Clauses 7.3 and 7.4 that all information must be capable of substantiation and such substantiation should be provided on request. Clause 7.4 also stated that substantiation need not be provided in relation to the validity of indications approved in the marketing authorization. It was possible to substantiate claims with unpublished data.

The Panel considered that the claim in question, 'Evista has reduced the incidence of newly diagnosed breast cancer in clinical trials', which appeared in both advertisements, gave the impression that women on Evista would be less likely to develop breast cancer. The Panel noted that Evista was intended for long-term use and the long-term effect of the product on the risk of breast cancer was not known. The claim had been derived from a statement in the SPC but did not reflect all of the data with regard to the effect of Evista on breast tissue in that the SPC also stated that the long-term effect of Evista on the risk of breast cancer was unknown. The Panel considered that the claim was therefore misleading. It was immaterial that the additional data was included in the prescribing information as it was an accepted principle under the Code that misleading claims etc could not be qualified by the small print. A breach of Clause 7.2 was ruled. This ruling applied to both advertisements.

The Panel noted that, in relation to the BMJ advertisement, the complainants had referred to Clause 6.2 of the Code which stated that where two pages of an advertisement were not facing, neither must be false or misleading when read in isolation. The Panel considered its ruling of a breach of Clause 7.2 in relation to both advertisements covered the allegation that the BMJ advertisement was in breach of Clause 6.2 and made no ruling in this regard. The claim in question was misleading irrespective of whether prescribing information was on the same page or not. The Panel noted that the physical separation of the prescribing information from the main body of the advertisement was not necessarily unacceptable under the Code.

APPEAL BY LILLY

Lilly acknowledged the Panel's comments that promotional material presented in different sizes and layouts should be separately certified and have unique reference numbers and would ensure that the guidelines in this regard would be complied with.

Lilly said that it had been most careful not to present data relating to breast cancer in a misleading way. For this reason it had tried to stay as close to the wording in the SPC as possible. Lilly made no claim about reducing the long-term risk of breast cancer, it simply stated the fact that 'Evista has reduced the incidence of newly diagnosed breast cancer in clinical trials'. By drawing attention to the fact that this information was taken from clinical trials, which were generally not long-term, Lilly considered that it had not been misleading and that any physician would know that this did not imply any long-term effect. The statement was referenced to the SPC rather than the 'small print' that the Panel referred to. The relevant facts were, however, also contained in the prescribing information which was part of the advertisement.

Lilly considered that the information was accurate, balanced, fair, objective and unambiguous and was not misleading directly or by implication.

APPEAL BOARD RULING

The Appeal Board noted Evista was indicated for the prevention of non-traumatic vertebral fractures in postmenopausal women at increased risk of osteoporosis. The indication section of the SPC stated that when determining the choice of Evista or oestrogen (hormonal replacement therapy) for an individual postmenopausal woman, consideration should be given to menopausal symptoms, effects on breast tissue, and cardiovascular risks and benefits.

The reader was then referred to section 5.1 of the SPC which was headed 'Pharmacodynamic properties'. Both section 5.1 of the SPC and the relevant section of prescribing information contained information regarding Evista's effect on breast tissue. Both documents stated that the long-term effect of Evista on the risk of breast cancer was unknown.

The Appeal Board noted that the advertisements had a theme of 'protection'. Each was headed 'Non-hormonal protection for post-menopausal women' and a strapline at the bottom of the advertisements read 'Non-hormonal protection'. Between the heading and the strapline appeared three claims of equal prominence about Evista. The first claim 'Evista prevents bone loss and reduces the risk of vertebral fracture' clearly related to the licensed indication for the product.

The third claim, 'Evista has reduced the incidence of newly diagnosed breast cancer in clinical trials', would, in the Appeal Board's view, also be seen as a licensed indication and another aspect of Evista's 'protection' for postmenopausal women. In addition the Appeal Board considered that the claim had not been put into context. It had not been clearly stated that the long-term effect of Evista on the risk of breast cancer was unknown.

The Appeal Board considered that the context of the claim at issue and its position within the advertisements meant that the advertisements were misleading with regard to the effect of the product on the incidence of breast cancer. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2.

The appeal was unsuccessful.

Complaint received **7 December 1998**

Case completed **30 March 1999**

CASES AUTH/812/12/98 and AUTH/813/12/98 *NO BREACH OF THE CODE*

HOSPITAL DRUG INFORMATION PHARMACIST v RHÔNE-POULENC RORER and MERCK PHARMACEUTICALS

Ikorel detail aid

A hospital drug information pharmacist complained about a detail aid for Ikorel (nicorandil) issued by Rhône-Poulenc Rorer and Merck Pharmaceuticals to which he and his cardiology consultants objected. National guidelines and general cardiology experience were that beta-blockers should always be used as the first choice in angina. In view of this, it was irresponsible to try to distract prescribers into using Ikorel as a first line medicine, particularly given its lack of mortality data. The British National Formulary was quoted in support of the complaint.

The Panel noted that the detail aid was entitled 'Think Ikorel First in Angina' and the phrase 'Think Ikorel first…' was repeated on each page. The Panel noted that the indication for Ikorel in its summary of product characteristics (SPC) was for the prevention and long-term treatment of chronic stable angina pectoris. There was no statement in the SPC to suggest that Ikorel could only be used as a second line medicine, for instance if the use of a beta-blocker were contraindicated. The Panel considered that the SPC did not prohibit the use of Ikorel as a first line agent. The Panel considered that the promotion of nicorandil as a first line treatment was not unacceptable and ruled no breach of the Code.

A hospital drug information pharmacist complained about the promotion of Ikorel (nicorandil) by Rhône-Poulenc Rorer. The material at issue was a detail aid (ref IKO101077) entitled 'Think Ikorel First in Angina'. The heading to every page in the detail aid began 'Think Ikorel first…' and each page had 'Think Ikorel first in angina' as a strapline. Nicorandil belonged to a class of medicines known as potassium channel activators. Ikorel was co-promoted by Rhône-Poulenc Rorer Limited and Merck Pharmaceuticals and the same detail aid was used in looseleaf format by Merck (ref ZZ08231).

Rhône-Poulenc Rorer and Merck submitted identical responses to the complaint.

COMPLAINT

The complainant provided a copy of the Ikorel detail aid to which he and his cardiology consultants strongly objected.

The complainant stated that the Authority and the manufacturers of Ikorel must be aware that national guidelines and general cardiology opinion was that beta-blockers should always be used as the medicines of first choice in angina. In view of this, it was irresponsible of the manufacturers of Ikorel to try to distract prescribers into using Ikorel as a first line medicine, particularly given its lack of mortality data.

To justify the complaint, the complainant quoted from the current British National Formulary (36 – September 1998).

> *'Stable angina* Acute attacks of stable angina should be managed with sublingual glyceryl trinitrate. If attacks occur more than twice a week, regular drug therapy is required and should be introduced in a stepwise manner according to response. Aspirin should be given to patients with angina; a dose of 75-150mg daily is suitable. Revascularisation procedures may also be appropriate.

Patients with mild or moderate stable angina who do not have ventricular dysfunction, may be managed effectively with sublingual glyceryl trinitrate and regular administration of a beta-blocker (Section 2.4). If necessary a long-acting dihydropyridine calcium-channel blocker (Section 2.6.2) and then a long acting nitrate (Section 2.6.1) may be added.'

It was alleged that the detail aid breached Clause 7 of the Code.

RESPONSE

Rhône-Poulenc Rorer and Merck stated that the indications for which Ikorel was licensed were stated in the summary of product characteristics (SPC). The product was indicated for 'the prevention and long-term treatment of chronic stable angina pectoris.'

The licensed indications agreed by the Medicines Control Agency (MCA) for Ikorel were broad and included its use as a first line treatment either as monotherapy or as combination therapy for the prevention and treatment of angina. It was important to note that the licence did not limit the use of Ikorel only to situations where the advice on treatment given in the British National Formulary had failed, namely as a second line add on therapy to treatment with a beta-blocker or when the use of a beta-blocker was inappropriate.

As a result of the terms set out in the marketing authorization for Ikorel granted by the MCA, Rhône-Poulenc Rorer and Merck could see no grounds for concluding that they had contravened Clause 7 of the Code by suggesting that doctors should 'Think Ikorel First in Angina'.

Notwithstanding this the companies clearly used the claim 'Think Ikorel First in Angina' throughout the detail aid as an important link to the key issues that a doctor must consider before prescribing an anti-anginal medicine for their patient. They did not claim that Ikorel must be used first, but suggested that it should be thought of first.

Finally, the companies agreed with the complainant that it was highly desirable to establish the effectiveness of anti-anginal products by determining their long-term efficacy by using the 'hard' endpoint of mortality. However, it was important to note that mortality assessment was not a requirement for product licensing authorization. Notwithstanding this, Rhône-Poulenc Rorer and Merck were currently sponsoring the IONA trial, which started in May 1998, investigating the long-term mortality effects of treating patients with Ikorel. The companies were not aware of evidence showing a mortality benefit for patients following treatment with any anti-anginal medicine licensed in the UK.

PANEL RULING

The Panel noted that the detail aid was entitled 'Think Ikorel First in Angina' and the phrase 'Think Ikorel first…' was repeated on each page of the detail aid. The Panel noted that the indication for Ikorel in its SPC was for the prevention and long-term treatment of chronic stable angina pectoris. There was no statement in the SPC to suggest that Ikorel could only be used as a second line medicine, for instance if the use of a beta-blocker were contraindicated. The Panel considered that the SPC did not prohibit the use of Ikorel as a first line agent. The Panel considered that the promotion of nicorandil as a first line treatment was not unacceptable and ruled no breach of Clause 7.2.

Complaint received **11 December 1998**

Case completed **12 February 1999**

CASE AUTH/814/12/98

GENERAL PRACTITIONER v UCB PHARMA

Conduct of a representative

A general practitioner complained about an activity which, to him, seemed to be becoming typical practice amongst medical representatives. The general practitioner had completed and returned a reply paid card to UCB Pharma requesting a copy of a textbook on dermatological surgery. When a representative called with the book she was told by the receptionist that the general practitioner was too busy to see her. Instead of leaving the book as suggested by the receptionist, the representative decided to call again with the book in the hope of seeing the complainant whom she had not met before.

The Panel considered that the representative was using the book as an inducement to gain an interview. A breach of the Code was ruled.

COMPLAINT

A general practitioner complained about an activity which seemed to him to be becoming typical practice amongst medical representatives.

The complainant stated that he had been sent a reply paid card (RPC) from UCB Pharma Limited regarding a free copy of 'An Introduction to Dermatological Surgery'. The completed RPC was provided. It seemed to the complainant as though the donation of medical literature was associated with a meeting with a general practitioner, which was of a promotional nature. The complainant specifically asked for a copy of the book in question. However, when a representative called on Friday, 27 November 1998, she said she was unable to leave a copy as she had instructions from head office that she would have to spend some time with the complainant before she could pass on this book.

The complainant considered that it was unacceptable to offer any sort of inducement of this nature which was conditional upon spending time discussing a pharmaceutical product.

RESPONSE

UCB stated that the representative in question confirmed that she had visited the complainant's practice on the date specified. No prior appointment had been made. On the morning in question, when the representative entered the practice, she informed the receptionist that she had a signed request from the complainant for a copy of a book on dermatological surgery and would it be possible to give it to him in person. She then presented the RPC to the receptionist. Her intention had been to request a spontaneous interview within the surgery with the complainant. The representative was fully aware that if such a request was refused she was required to leave the book behind for the doctor.

UCB stated that the receptionist politely informed the representative that the complainant was very busy seeing patients, therefore, it would not be possible for her to see him. However, the receptionist then added that she could leave the item behind. The representative replied that as she was new to the area, and as she had never met the complainant before, would it be possible for her to call again with the book? The receptionist replied that the complainant was 'a little funny about such things' but if she could leave behind her contact details she would pass the message on. Accordingly, the representative left behind the RPC, her mobile telephone number and business card. At no time during the course of the visit did either the representative or the receptionist talk to the complainant, therefore, at no time during the visit did he refuse or accept the representative's request. Had he done so, either directly to her or via the receptionist, she was quite clear that the correct action would be to leave the book with the receptionist. The representative considered that the conversation with the receptionist was conducted in a friendly, professional and polite manner by both sides. The fact that she had left behind the RPC and her full contact details demonstrated the openness of her approach. At no time had she stated or intimated that the receipt of the book was conditional on being granted an interview.

UCB explained that later that morning the representative received a telephone call from the complainant who was obviously angry and upset. He informed her that he thought that 'her professional behaviour was disgusting and that an RPC was not to be used as blackmail.' Although at the time the representative was extremely upset about the allegation, and the manner in which it was directed at her, she politely expressed her regret that she had inadvertently made such an impression upon him. When she then asked if she could contact head office about the matter the complainant informed her that she 'could do whatever she wanted and that he was reporting her to the ABPI.'

UCB submitted that with regard to the complainant's statement that 'she said she was unable to leave a copy for me as she had instructions from head office that she would have to spend some time with me before she could pass on this book' the representative wished to state, in the strongest possible terms, that she had never made such a statement, either to the complainant or the receptionist.

UCB stated that the use of RPCs offering an item that would be of use to healthcare professionals was in its opinion, a common industry practice. Companies offered this service because they hoped it would help to draw attention to the company or its products, and also to assist medical representatives in making a face-to-face contact with doctors. However, it was quite clear that if the RPC and book was used in the manner as described by the complainant there would have been a clear breach of Clause 15.3 of the Code.

UCB stated that it was the representative's judgement at the time that, as her request to see the complainant had not actually been refused by him during the course of the visit, it was not unreasonable under the circumstances to offer to deliver it at another more convenient time. She did appreciate however that it was clear from the complaint that he was unlikely to have granted such a request. Therefore, in hindsight, it was clear that the book should have been left behind, but at the time of her visit the representative did not know this, particularly as she had never had any previous direct or indirect contact with the complainant. Furthermore, she had readily agreed to pass on her contact details, including the RPC, to the receptionist when so requested therefore there were no grounds to believe that during the course of her visit she employed, or attempted to employ, any subterfuge to obtain an interview.

UCB considered that, based upon the representative's account of events and intentions, there was a reasonable case for suggesting that Clause 15.3 was not breached. As there was no reason to believe that the representative's actions were either disrespectful or discourteous during the course of the visit, or the subsequent telephone conversation, UCB did not consider that she had breached either Clause 9.1 or 15.2.

UCB gave details about when the representative had joined the company. The representative had yet to sit the ABPI Medical Representatives Examination.

UCB supplied a copy of the book in question together with the relevant invoice. The company considered the book complied with the requirement of Clause 18 of the Code. It was inexpensive (£5.47 per copy) and relevant to the practice of medicine as required under Clause 18.1. The book did not mention any of UCB's products, and /or competitors' products. Prescribing information did not accompany this (Clause 18.3). Clearly the book was not offered as an inducement to prescribe, supply, administer or buy any of UCB's products (Clause 18.1). Briefing notes were not produced as it was a general item which did not involve any mention of UCB's products and/or competitors' products. UCB explained that detailed briefing materials were normally only issued for items involving the technical or medical aspects of its products, as required by Clause 15.9 of the Code. However, all representatives underwent in-house training concerning the Code by means of a presentation from a member of the Medical Department, and the use of role playing exercises which included the correct and proper use of RPCs. According to the company's records the representative concerned had attended such a course.

UCB concluded that it was clear that on hindsight the representative should have left the book with the receptionist. However, in view of the representative's account of the visit, the company considered that on balance there was reasonable cause for suggesting that Clause 15.3 was not breached. Furthermore, the company considered that Clauses 9.1, 15.2 15.3 15.8 and 18 were not breached.

PANEL RULING

The Panel noted that the original RPC provided by the complainant showed that he had ticked the statement "Yes, I would like to receive a copy of 'An Introduction to Dermatological Surgery'", stamped the card with the surgery stamp and signed the card. The request for a sample of Zirtek and the statement 'The best time to call is' were left blank. The Panel accepted that items offered on mailings were often delivered by representatives but noted that if a doctor was not available or did not want to see the representative, the item had to be left for the doctor, otherwise it became an inducement to gain an interview in breach of Clause 15.3 of the Code.

The Panel noted that the representative arrived at the complainant's surgery without an appointment to see him. The receptionist explained to the representative that the complainant was too busy to see her and suggested that she leave the book behind. The representative decided not to, suggesting instead that she would call again with the book in the hope of seeing the complainant, whom she had not met before. The Panel considered that the representative was clearly using the book as an inducement to gain an interview with the complainant. It was immaterial that on the day the complainant did not personally, or through his receptionist, refuse the representative's suggestion of a second visit. A breach of Clause 15.3 was ruled.

During its consideration of this case the Panel noted that Clause 18.2 of the Code stated that gifts in the form of promotional aids, whether related to a particular product or of general utility, could be distributed to members of health professions, provided that such gifts were inexpensive and relevant to the practice of their profession. Inexpensive was defined in the supplementary information to Clause 18.2 as costing the donor company no more than £5 excluding VAT. The Panel queried whether the book in question was acceptable as a promotional aid as each copy had cost the company more than £5 (VAT was not charged on books). The Panel noted that the title page of the book carried the statement 'Sponsored by UCB Pharma'. There was no product branding of the book. The Panel, however, did not consider that the book could claim the benefit of the exemption in the supplementary information to Clause 18.1 (provision of medical and educational goods and services) as its distribution was too closely linked to promotion. It appeared that it had been offered on a Zirtek mailing as the RPC offered a sample of Zirtek. The Panel requested that UCB be informed of its views in this regard.

Complaint received **14 December 1998**

Case completed **17 February 1999**

GENERAL PRACTITIONER v GLAXO WELLCOME

Reply paid card offering gift

A general practitioner said that he had noticed a new marketing ploy being used by pharmaceutical companies whereby they offered a practice aid and asked for a time to deliver it. The complainant understood that if a doctor requested a practice aid, this did not have to be dependent on the doctor seeing a representative. A reply paid card from Allen & Hanburys was provided which stated 'Please send this card back to us… and we will deliver a box full of teddy badges like these for your young patients'. It went on to say 'Best time to deliver; in the afternoon if at all possible?' with spaces for the insertion of the day, time, signature and date.

The Panel noted that the Appeal Board had recently expressed the view that if reply paid cards referred to representatives delivering items, then recipients should be given an alternative delivery option or an explanation that there was no obligation to grant the representative an interview when the item was delivered. This was to avoid giving the impression that there was such an obligation.

The Panel could understand the complainant's concern in this case but on balance considered that the reply paid card was not unacceptable. Unlike previous cases it did not actually refer to representatives delivering the items. In the Panel's view it was written in such a way that readers would not assume that they were obliged to see the representative in order to receive the gift. The company's instructions to representatives were clear in that items had to be left if the doctor refused to see the representative. No breach of the Code was ruled.

A general practitioner complained about a reply paid card provided by Allen & Hanburys. The reply paid card (ref HM5059-FP/October 1998) was part of a Flixotide mailing. The card offered a box of teddy badges for younger patients. The reply paid card stated: 'Please send this card back to us… and we will deliver a box full of teddy badges like these for your young patients'. It went on to say 'Best time to deliver; in the afternoon if at all possible?' with spaces for the insertion of the day, time, signature and date.

COMPLAINT

The complainant stated that over the last few months he had noticed a new marketing ploy being used by pharmaceutical companies whereby they offered a practice aid and then ask for a time to call to deliver it. The complainant's understanding of the regulations was that if a doctor requested a practice aid, this did not have to be dependent on that doctor agreeing to see the representative.

The complainant asked for this to be confirmed and if necessary action taken towards the pharmaceutical companies concerned. The complainant provided an example of a reply paid card from Allen and Hanburys.

RESPONSE

Glaxo Wellcome stated that naturally it would be concerned if some companies were using unreasonable methods to gain interviews with doctors and sympathised with the complainant if this was the case.

The reply paid card provided by the complainant was enclosed with a letter promoting the use of Flixotide (fluticasone propionate) in children with asthma.

Glaxo Wellcome was very aware of the pressure on a doctor's time and was careful not to build any preconditions into the wording on reply paid cards associated with offers of practice items. Hence the wording on the card in question.

Glaxo Wellcome submitted that there were no pre-conditions regarding the delivery of the badges being conditional on an interview with the receiving doctor. The representatives all understood that if a doctor was not available to see them then any requested items would be left with the doctor's nominee. Naturally, the visit to deliver the badges might provide an opportunity to arrange with the receptionist for a subsequent appointment with the doctor.

Glaxo Wellcome submitted that the reply paid card and the offer itself did not represent any inducement or subterfuge to gain an interview and there was no breach of Clause 15.3 of the Code.

Specific briefing instructions were not provided to representatives for this particular item. However the company's general instructions regarding the delivery of practice items were in its document 'ABPI Code of Practice – Guidance for Representatives'. A copy was provided.

PANEL RULING

The Panel noted that there had been two recent complaints regarding the wording on reply paid cards. Case AUTH/646/11/97 concerned an offer of a calendar and the reply paid card stated that a representative would deliver the item. A space was provided for the doctor to complete to indicate the day and time that would be most convenient. A breach of Clause 15.3 of the Code had been ruled by the Appeal Board as it was considered that readers would assume that to receive the calendar they were obliged to see the representative and this was unacceptable.

Cases AUTH/695/4/98 and AUTH/696/4/98 concerned the offer of a mini dictaphone. The reply paid card stated that 'I would like a representative to deliver my complimentary mini dictaphone' followed by a box to tick. The Appeal Board considered that readers would assume that in order to receive the mini dictaphone they were obliged to see the representative. This was unacceptable. No other option had been given. A breach of Clause 15.3 of the Code was ruled.

In the Appeal Board's view, if reply paid cards referred to representatives delivering items then recipients should be given an alternative delivery option or an explanation that there was no obligation to grant the representative an interview when the item was delivered. This was to avoid giving the impression that there was such an obligation. The Appeal Board's view had been included in the November edition of the Code of Practice Review but because late changes had to be made to the editorial section, this had not been issued until January.

Turning to the case now before it (Case AUTH/815/12/98) the Panel noted that the card made no reference to the method of delivery only that '…we will deliver…' and space was left for indicating the best time to deliver.

The Panel noted that Glaxo Wellcome's guidance for representatives (dated 6 August 1997) clearly instructed representatives in relation to the requirements of Clause 15.3 of the Code that 'If, however, the doctor refuses an interview at the time of delivery, the material should be left with a receptionist or assistant, and should not be taken away, otherwise the material could be regarded as an inducement to gain an interview.'

The Panel could understand the complainant's concern but on balance considered that the reply paid card was not unacceptable. Unlike the previous cases it did not actually refer to representatives delivering the items. In the Panel's view it was written in such a way that readers would not assume that they were obliged to see the representative in order to receive the gift. The company's instructions to representatives were clear in that items had to be left if the doctor refused to see the representative. No breach of Clause 15.3 the Code was ruled.

Notwithstanding the ruling, the Panel considered that Glaxo Wellcome should be advised to follow the Appeal Board's view, as set out above, in any future such cards, whether or not representatives were actually mentioned.

Complaint received **18 December 1998**

Case completed **12 February 1999**

CASE AUTH/816/12/98 *NO BREACH OF THE CODE*

HEALTH AUTHORITY PRIMARY CARE MEDICAL ADVISER v BRISTOL-MYERS SQUIBB

Dutonin 'Dear Health Professional' letter

The primary care medical adviser at a health authority complained about a 'Dear Health Professional' letter for Dutonin (nefazodone) which had been sent by Bristol-Myers Squibb. The letter featured a comparison of the cost of newer antidepressants with that of Dutonin. The comparison was not in terms of money but gave the number of patients who could be placed on Dutonin compared with 100 patients on each of the five competitor products mentioned, the Dutonin figure being greater than 100 in each case.

The complainant considered that the letter was very simplistic in its message but he thought that it was advertising a totally irrational approach to prescribing, based on cost and not on clinical effectiveness.

The Panel noted that promotion on the basis of price alone was not unacceptable. The Panel did not consider that the manner in which costs had been compared in the letter implied that more patients should be put on Dutonin without any regard to need or clinical effectiveness as alleged. No breach of the Code was ruled.

The primary care medical adviser at a health authority complained about a Dutonin (nefazodone) 'Dear Health Professional' letter sent by Bristol-Myers Squibb Pharmaceuticals Limited to general practitioners, psychiatrists and NHS personnel/pharmacists as a follow up to a previous mailing. The letter featured a comparison of the cost of newer antidepressants with that of Dutonin. The competitor products were sertraline, venlafaxine, mirtazapine, paroxetine and fluoxetine. The comparison was not in terms of money but gave the number of patients who could be placed on Dutonin compared with 100 patients on each of the five competitor products mentioned. In all cases the figure stated for Dutonin was more than 100. It was stated that the comparisons assumed that patients were on recommended maintenance doses and concomitant prescribing was not required. Readers were instructed to refer to an enclosed leaflet entitled 'Antidepressant therapy that keeps down cost' for further details.

The leaflet included a table comparing the per patient cost of six months' treatment at stated standard doses of each of six antidepressants with that of Dutonin. The comparison included the five products mentioned in the letter and in addition reboxetine was included. The percentage difference in cost to Dutonin was noted and ranged from +58% to +10%. A second table detailed the daily cost range for seven antidepressants (the six products included in the first table plus citalopram) with that of Dutonin. The lowest daily costs ranged from 60 pence/day for Dutonin and citalopram to 94 pence/day for sertraline. For all the antidepressants other than Dutonin the maximum cost of each antidepressant included an additional cost of 24 pence/day for the co-prescription of a hypnotic. This was done on the basis that co-prescription of a hypnotic should not be necessary with Dutonin as Dutonin was indicated to treat sleep disturbances which might accompany depression.

COMPLAINT

The complainant stated that the letter was very simplistic in its message but he thought it was advertising a totally irrational approach to prescribing, based upon cost, and not upon clinical effectiveness. Whilst the letter did no more than justify this, the complainant thought it was an extremely unhelpful kind of comment to make because the immediate impact and implication of it was that more patients should be put on to Dutonin without any regard for the need or clinical effectiveness of treating these patients.

RESPONSE

Bristol-Myers Squibb stated that the letter provided a direct comparison of numbers of patients that could be treated for the same cost with Dutonin compared with other commonly prescribed antidepressants on the market. This was a pure cost comparison between the products based on the November 1998 MIMS prices as referenced, and based on the cost of the recommended maintenance dose of each treatment. An example calculation showed that the recommended maintenance dose of Dutonin was taken to be 200mg bd at a cost per patient per month of £16.80. The company considered that it was comparing like with like in accordance with Clause 7.2.

Bristol-Myers Squibb stated that the medicines in the comparison were all indicated for depression and were representative of those currently prescribed for this indication. All of the medicines had been shown to be clinically effective in depression. Therefore, the company did not agree that it was suggesting clinicians should disregard clinical effectiveness. Moreover, Bristol-Myers Squibb considered that there was nothing in the letter that encouraged the clinician to disregard the clinical requirements of the individual patient and take a 'totally irrational approach' to prescribing.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2 (price comparisons) stated that price comparisons must be accurate, fair and must not mislead. Valid comparisons could only be made where like was compared with like. A price comparison should be made on the basis of the equivalent dosage requirement for the same indication.

The Panel noted that the summary of product characteristics for Dutonin stated that the usual therapeutic dose was 200mg twice daily. From the example calculation it could be seen that this was the dose which had formed the basis of the calculations. The corresponding 'recommended' or 'usual' daily doses of the other products were sertraline 50mg; venlafaxine 75mg; mirtazapine 30mg; paroxetine 20mg and fluoxetine 20mg (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998-99) and were the lowest doses of each. This had been stated in the leaflet which accompanied the letter.

The Panel noted that the leaflet compared the antidepressants in terms of cost but pointed out the percentage difference in cost compared with Dutonin. There was a +58% difference in the cost of sertraline. Consequently the letter stated that 'For every 100 patients on sertraline, you could put 158 on Dutonin'. In the Panel's view the letter expressed in terms of patients exactly the same information as the leaflet expressed in terms of money.

The Panel noted that promotion on the basis of price alone was not in itself unacceptable. The Panel did not consider that the manner in which costs had been compared in the letter implied that more patients should be put on Dutonin without any regard to need or clinical effectiveness as alleged. No breach of Clause 7.2 was ruled.

During its consideration of this case, the Panel noted that the letter and one of the two tables in the leaflet both showed Dutonin as less expensive than the other antidepressants listed, which did not include citalopram. The other table in the leaflet, however, showed that if co-prescribing of a hypnotic was not required, then 20mg citalopram daily cost the same as 400mg Dutonin daily. The Panel questioned whether a basis of selection which excluded citalopram could be considered a fair one and asked that its concerns be drawn to the attention of Bristol-Myers Squibb.

The Panel also noted that the only date of preparation on the 'Dear Health Professional' letter was July 1997 although one reference was given as MIMS, November 1998. The leaflet carried a date of preparation of April 1998 and prices were referenced to MIMS, April 1998. The stated price of citalopram, however, was not that given in MIMS, April 1998, as at that time the product was more expensive. The correct current cost of citalopram had been given in the leaflet. Cost comparison should always be based on current costs. The Panel noted that Clause 4.7 of the Code required all promotional material other than advertisements appearing in professional publications to include the date on which the promotional material was drawn up, or last revised. There were discrepancies in dates, references and costs stated and the Panel requested that these be brought to the attention of Bristol-Myers Squibb.

Complaint received **21 December 1998**

Case completed **25 February**

CASE AUTH/826/1/99

DIRECTOR/PARAGRAPH 16 v SERVIER

Natrilix SR leaflet

During its consideration of Case AUTH/792/11/98 concerning a leaflet for Natrilix SR (indapamide 1.5mg), the Panel considered that a list of primary and secondary objectives of the HYVET study (hypertension in the very elderly trial) which appeared on the front page of the leaflet gave the impression that Natrilix was licensed to reduce stroke, stroke mortality, cardiac mortality and cardiovascular mortality, whereas it was actually licensed only for hypertension. The Panel decided that the matter should be taken up with Servier under the provisions of Paragraph 16 of the Constitution and Procedure.

The Panel noted that Natrilix was indicated for the treatment of hypertension. The Panel considered that the leaflet gave the impression that the stated objectives of the trial were licensed indications for Natrilix. This was not so. The Panel ruled a breach of the Code.

COMPLAINT

During its consideration of Case AUTH/792/11/98 concerning a leaflet (ref 99NX1C101) for Natrilix SR (indapamide 1.5mg), the Panel considered that a list of primary and secondary objectives of the HYVET study (hypertension in the very elderly trial) which appeared on the front page of the leaflet gave the impression that Natrilix was licensed to reduce stroke, stroke mortality, cardiac mortality and cardiovascular mortality whereas it was actually licensed only for hypertension. The Panel decided that the matter should be taken up with Servier Laboratories Ltd under the provisions of Paragraph 16 of the Constitution and Procedure in relation to the requirements of Clause 3.2 of the Code.

RESPONSE

Servier noted that the promotional piece in question was a four page information card, the first page of which was labelled 'Fact Sheet'. The page gave the main features of the HYVET study, a major hypertension trial addressing an as yet unanswered question, namely the benefit of blood pressure reduction in patients over the age of 80 years. The page included a list of the primary and secondary objectives of the study – stroke, stroke mortality, cardiac mortality and cardiovascular mortality, recognised major sequelae of untreated hypertension.

The justification for treating hypertension was to reduce the risk of these events occurring and it was therefore implicit in the prescribing of an anti-hypertensive agent that the agent was being prescribed to improve prognosis by reducing the risk of major cardiovascular sequelae. In the company's view, it could not be considered a breach of the Code to discuss these sequelae as objectives of a study concerning an anti-hypertensive.

Servier found it difficult to understand how the Panel came to consider that the list of these objectives gave the impression that Natrilix was licensed to reduce stroke, stroke mortality, cardiac mortality and cardiovascular mortality.

Servier pointed out that:

1) the page was presented as a Fact Sheet;

2) the page contained no brand name or logo for Natrilix SR, the only relevant mention being the fourth bullet point under 'Design', 'active treatment: indapamide 1.5 mg', which was in the same type size as all other information on the Fact Sheet;

3) details of the trial, including objectives, power, start and finish dates were clearly given;

4) stroke, stroke mortality, cardiac mortality and cardiovascular mortality were clearly listed as the objectives of the study. Servier did not intend that these should in any way constitute claims or indications, nor did Servier consider that the page could give this impression.

The Panel had already ruled, in considering the initial complaint, that the primary and secondary objectives of the HYVET study were clearly and prominently labelled as such, that the start and finish dates of the trial were provided and that the page was not misleading. It was clear that the list was of objectives in a clinical trial, it seemed to Servier to be inconsistent to consider that they could also give the impression that they were indications.

Servier did not consider this leaflet to be in breach of Clause 3.2 of the Code.

PANEL RULING

The Panel noted that the leaflet consisted of four pages. The second, third and final pages of the leaflet featured promotional claims for Natrilix. The front page, in highlighted boxes, stated the design and objectives of the HYVET study as bullet points in bold type. The fourth bullet point in the design section stated 'active treatment: indapamide 1.5mg'. In the objectives section the percentage reduction in each of the objectives that the study was powered to detect was stated, ie a 35% reduction in stroke, a 60% reduction in stroke mortality, a 50% reduction in cardiac mortality and a 35% reduction in cardiovascular mortality.

The Panel noted that Case AUTH/792/11/98 concerned an allegation that the front page of the leaflet gave the misleading impression that the HYVET study was complete, the percentage reduction of each study objective representing actual trial results. The Panel did not consider that the page was misleading as alleged, the trial objectives were clearly and prominently labelled as such. No breach of the Code was ruled.

The Panel noted that Natrilix was indicated for the treatment of hypertension. The Panel considered that the leaflet gave the impression that the stated objectives of the trial were licensed indications for Natrilix. This was not so. The Panel ruled a breach of Clause 3.2 of the Code.

Proceedings commenced 22 December 1998

Case completed 18 February 1999

CASE AUTH/827/1/99

HEALTH AUTHORITY PRIMARY CARE MEDICAL ADVISER v YAMANOUCHI PHARMA

Men's Health Matters – public awareness campaign

A health authority primary care medical adviser complained about a public awareness campaign, Men's Health Matters, sponsored by Yamanouchi Pharma. A 'Dear Doctor' letter explained that the campaign was intended to provide information on health problems commonly experienced by men and to encourage them to seek health advice sooner. An A4 poster 'Male Over 50 Prostate Problems?' gave the symptoms of prostate problems and said that most could be treated with medicines. The poster referred to an information leaflet entitled 'Waterworks'. This leaflet gave general information about the prostate gland and discussed the treatment of prostatitis, benign prostatic hyperplasia (BPH) and prostate cancer. In the section on BPH three treatment options were explained and it was stated that a number of drugs could improve BPH symptoms by relaxing the muscle cells within the prostate gland.

The complainant had been provided with the material by a local general practitioner who considered that it was a clever bit of advertising of prescription only medicines to the general public. The GP had not been surprised to see that the campaign was funded by Yamanouchi Pharma, the manufacturers of tamsulosin (Flomax MR). He wondered whether it was legal. Even if it was it should not be encouraged.

The Panel noted that the 'Dear Doctor' letter informed GPs of the launch of the campaign within their area and alerted them to the fact that prostate assessment clinics had been set up locally. The letter made no direct or implied reference to any class of medicine or any specific medicine. The letter was signed on behalf of Men's Health Matters and clearly indicated that it was supported by an educational grant from Yamanouchi. The Panel considered that the letter was not promotional and no breach of the Code was ruled.

In relation to the poster, and a leaflet with a similar text, the Panel noted that a complaint about a similar leaflet had been considered previously and no breach of the Code had been ruled (Case AUTH/802/11/98). There had been no appeal in that case and, as provided for in the Constitution and Procedure, the new complaint was allowed to proceed. The Panel considered that the leaflet and poster raised public awareness about prostate problems and the fact that they could be treated with medicines. Both might facilitate the market development of Flomax MR. The Panel did not consider that either the leaflet or the poster was an advertisement for the product to the general public. The Panel accepted that the leaflet and the poster might encourage patients to discuss prostate problems with their doctor but neither encouraged patients to ask their doctors to prescribe a specific medicine. No breach of the Code was ruled.

In relation to the 'Waterworks' leaflet, the Panel noted that in the section of the leaflet dealing with BPH a sub-section entitled 'Relaxing the gland with drugs' referred to a number of drugs that could improve BPH symptoms by relaxing the muscle cells within the prostate gland. The leaflet referred to the disadvantages of the earlier medicines which might cause an increase in side effects in people already taking medication to control hypertension. The leaflet went on to state that 'Fortunately, a new class of drug, the alpha1A-adrenoceptor antagonists, has recently been developed specifically to treat BPH'.

The Panel did not consider that the 'Waterworks' leaflet was an advertisement to the general public for a prescription only medicine *per se* and ruled no breach of the Code in that regard. Nevertheless, in the Panel's view, the statement regarding alpha1A-adrenoceptor antagonists would encourage patients to ask their doctors to prescribe such a medicine which in effect would lead to a prescription for Flomax MR. A breach of the Code was ruled.

A health authority primary care medical adviser complained on behalf of a local general practitioner about a public awareness campaign, Men's Health Matters, sponsored by Yamanouchi Pharma Ltd. Material provided by the complainant included a 'Dear Doctor' letter which explained that the campaign was for people with prostate problems and aimed to provide information on health problems commonly experienced by men and to encourage them to seek health advice sooner. Details of support material and services available, including a telephone helpline, were provided; it was stated that posters and leaflets were available from Yamanouchi. The 'Dear Doctor' letter included the statement 'Supported by an educational grant from Yamanouchi Pharma Ltd'.

An A4 poster entitled 'Male Over 50 Prostate Problems?', was also provided by the complainant. The poster, in a series of questions to the reader, gave the symptoms of prostate problems and stated "No, it isn't 'your age', and something simple can be done about it. Most prostate problems can be treated with medicines. Ask your doctor for help". At the bottom of the poster was a logo, MHM, and 'Men's Health Matters'. The poster referred to an information leaflet entitled 'Waterworks'. In its response to the complaint

Yamanouchi additionally supplied an A5 leaflet with text similar to that of the poster. Instead of the statement 'Ask your doctor for help' however, the leaflet read 'Your doctor will be able to help. Ring the surgery NOW to make an appointment.' The leaflet did not refer to the 'Waterworks' leaflet. Neither the poster nor the leaflet gave the telephone number of the helpline.

The 'Waterworks' leaflet, supplied by the complainant, gave general information about the prostate gland and discussed the symptoms and treatment of prostatitis, benign prostatic hyperplasia (BPH) and prostate cancer. The risk of developing each condition according to age was discussed and finally a list of the names and addresses of relevant charities and patient help groups was given. In the section on BPH, it was explained that the condition was treated in three ways, surgery, shrinking the gland with drugs or relaxing the gland with drugs. An explanation of each treatment option was given. It was stated that 'A number of drugs can improve BPH symptoms by relaxing the muscle cells within the prostate gland'.

Yamanouchi marketed Flomax MR (tamsulosin), a selective alpha1A-adrenoceptor antagonist for the treatment of functional symptoms of BPH.

COMPLAINT

The complainant provided a copy of a letter which had been sent to him by a local general practitioner. The general practitioner drew attention to what he considered was a clever bit of direct advertising of prescription only medicines for the general public. A copy of the relevant publicity from 'Men's Health Matters' was provided. The GP's view was that on reading the poster it seemed fairly clear that the advice ('Most prostate problems can be treated with medicines') had a promotional flavour to it. The GP was not surprised to see that the campaign was financed by Yamanouchi Pharma Ltd, the manufacturers of tamsulosin. The GP wondered whether this sort of direct (though admittedly implied) advertising was legal. Even if it was, presumably it should not be encouraged. The GP queried whether the health authority should at least discourage this particular advertisement maybe by circular to local practices.

The complainant questioned the acceptability of the promotional material and queried how close to the line it might be.

When writing to Yamanouchi the Authority drew attention to the provisions of Clauses 9.9, 20.1 and 20.2 of the Code.

RESPONSE

Yamanouchi provided background information to the Men's Health Matters (MHM) campaign explaining that a 1997 Gallup survey conducted in the UK had shown that the majority of men with health issues did not seek early medical attention because they were either too embarrassed to consult their GP about their symptoms, or they considered that symptoms caused by certain diseases were part of the normal ageing process, with no available medical treatment.

The MHM campaign was a health education campaign which primarily addressed men's health issues which hit 'below the belt', in particular symptoms of prostate disease. The objective of the campaign was to reassure men who might have symptoms suggestive of urogenital disease that medical advice and help was available. By encouraging men concerned about their health to visit their local health professional sooner rather than later, potentially serious morbidity and mortality could be reduced or avoided. Yamanouchi explained that the campaign was funded by an educational grant from the company, and involved a charity and an agency in the delivery of the campaign.

The charity was a registered independent charity staffed by trained nurses registered by the Royal College of Nursing. The charity ran various telephone advice lines for the general public offering advice on issues such as heart disease, lifestyle matters, obesity and prostate problems. One of the advice lines was for men's health which was the same as the MHM telephone advice line referred to in the 'Waterworks' leaflet and the 'Dear Doctor' letter. [This was not the same telephone number as that given on the leaflet which was the subject of Case AUTH/802/11/98. That telephone helpline stated in its introduction 'This is a free service brought to you by Yamanouchi Pharma.] The MHM advice line provided professional advice and information over the telephone on all aspects of medical and healthcare matters. The quality of advice given to callers was routinely monitored and the nurses did not diagnose or recommend particular medicines to callers using the service. The nurses were supplied with a copy of the ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998-99 for reference. A nurse might post the 'Waterworks' leaflet to a caller when appropriate.

The brief that had been given to the nurses on how to answer telephone queries from the general public was provided as was a copy of the charity's mission statement and background information on the charity organisation including a list of advisors who acted in a training capacity. Yamanouchi also provided details of its financial support to the charity.

Yamanouchi stated that another pharmaceutical company which was also involved in marketing a medicine for the management of BPH was currently circulating a patient educational leaflet advertising the services of the MHM telephone advice line. In its leaflet, patients were requested to contact MHM by post or to use the MHM telephone advice line for additional information about prostate symptoms and diseases. Calls were handled identically by the charity regardless of how the caller obtained the advice line number.

Yamanouchi stated that the agency, on behalf of Yamanouchi, wrote and produced all the printed materials which were at issue. Normal commercial arrangements with respect to costs applied.

Yamanouchi explained that the campaign might only be launched and implemented in a particular health authority after consent and full agreement by the local hospital urology team. Once this had been obtained, all the local GPs who routinely referred patients to the hospital urology department were sent a 'Dear

Doctor' letter, along with the 'Male Over 50 Prostate Problems?' poster and leaflet, and a supply of the 'Waterworks' leaflet. The 'Dear Doctor' letter advised GPs of the existence of a Prostate Assessment Clinic (PAC) at their local hospital and explained the benefits of the MHM campaign as a whole.

With regard to specific pieces of material Yamanouchi provided the following explanations:

1 'Dear Doctor' letter

This letter informed the GP of the campaign in general and of the existence of a PAC at their local hospital. Yamanouchi explained that PACs helped to streamline the assessment of patients with prostate symptoms, reduced outpatient referral times and improved medical care and services offered to patients with prostate disease. This was an added value service which had not only enhanced patient satisfaction with the new NHS but, more importantly, reduced patient anxiety about the potentially life-threatening implications such as prostate cancer. PACs were co-ordinated and managed by the local urology consultant(s) in conjunction with a team of urology nurse(s) employed by the local hospital. Yamanouchi might assist in the running of these PACs by giving unconditional financial support to the hospital urology department. How the department chose to utilise the donation was up to the consultant in conjunction with the health authority but was documented for Yamanouchi's information. Services funded included bladder scanners or patient record forms.

Yamanouchi considered this letter not to be of a promotional nature and therefore not within the scope of the Code.

2 'Male Over 50 Prostate Problems?' leaflet and poster

Yamanouchi referred to Case AUTH/802/11/98 stating that the leaflet and poster had previously been subject to a complaint which was considered by the Panel, which found that these materials were not in breach of Clauses 20.1 or 20.2 of the Code.

3 'Waterworks' leaflet

Yamanouchi stated that this was a non-promotional educational leaflet which contained information for the public concerning men's health issues, specifically prostate diseases. Topics covered in the leaflet included common symptoms associated with prostate cancer, prostatitis, benign prostatic hyperplasia (BPH) and advice on available disease management. There was no mention of specific medicines or products promoted by any pharmaceutical company actively involved in the urology therapy area.

Yamanouchi explained that the 'number of drugs' which could improve BPH symptoms as referred to in the leaflet related to all alpha-blockers which were licensed to treat urinary symptoms due to BPH. Alpha-blockers which fell under this umbrella included doxazosin, indoramin, terazosin, alfuzosin, tamsulosin and prazosin. Yamanouchi stated that prazosin, indoramin, doxazosin and terazosin might increase the risk of hypotensive side effects such as syncope, and fractures due to falls, in patients who were already receiving antihypertensives, especially the elderly. These medicines required dose titration and careful monitoring of blood pressure to avoid the risks of first dose hypotension.

Yamanouchi stated that the alpha1A-adrenocepters were thought to predominate both functionally and numerically in the human prostate and were involved in prostatic smooth muscle contraction. Antagonism of these receptors reduced smooth muscle contractility in the prostate and urethra which decreased outflow obstruction and improved urinary symptoms of BPH. A number of alpha-blockers, originally developed as antihypertensives, might increase the risk of hypotensive side effects due to their relative activity on the alpha1B-receptor subtype located in the peripheral vascular system. This alpha1 subtype was thought to be responsible for blood pressure homeostasis.

Yamanouchi stated that *in vitro* and *in vivo* data had demonstrated that newer alpha-blockers such as alfuzosin and tamsulosin had a relatively greater selectivity and affinity for the alpha1A-receptor vs the alpha1B-receptor compared with older alpha-blockers such as terazosin and prazosin. Double-blind, randomised, placebo-controlled and comparative clinical trials had shown that these newer alpha-blockers had a reduced risk of hypotension and this was reflected in the relevant summaries of product characteristics (SPCs). It appeared that this was due to their greater selectivity for the alpha1A-receptor. However the selectivity for the alpha1A-receptor varied. The alfuzosin SPC stated: "…antihypertensive agents should be used with caution because of the risk of a hypotensive effect'. No such warning existed in the tamsulosin SPC.

In conclusion Yamanouchi stated that the MHM campaign had been in operation since April 1998 and to date the response from both the public and health professionals had been one of encouragement and gratitude. Yamanouchi considered that these initiatives added a valued service to the public, attempting to demystify health concerns and further educating people about their health. The company refuted any suggestion that the campaign in general or the items used breached Clauses 20.1 and 20.2 of the Code. The materials as described above were non-promotional, balanced and did not encourage members of the public to ask their doctor for a particular medicine.

Yamanouchi stated that with respect to Clause 9.9 the materials used in the MHM campaign were of a non-promotional nature. The company noted the Panel's comments in Case AUTH/802/11/98 regarding declaration of sponsorship of the three items ('Male Over 50 Prostate Problems?' leaflet and poster and 'Waterworks' leaflet) and it had been decided that at the next reprint, all materials would contain information that the campaign was sponsored by an educational grant from Yamanouchi.

PANEL RULING

1 'Dear Doctor' letter

The Panel noted that the 'Dear Doctor' letter informed GPs of the launch of the MHM campaign within their area and alerted them to the fact that prostate

assessment clinics had been set up locally. The letter made no direct or implied reference to any class of medicine or any specific medicine. Details of support materials and the number of the telephone helpline were given. The letter was signed on behalf of Men's Health Matters and clearly indicated that it was supported by an educational grant from Yamanouchi. The Panel considered that the letter was not promotional. No breach of the Code was ruled.

2 'Male Over 50 Prostate Problems?' leaflet and poster

The Panel noted that in Case AUTH/802/11/98 its ruling of no breach of Clauses 20.1 and 20.2 of the Code in relation to the A5 leaflet had not been appealed by the complainant. In accordance with Paragraph 5.1 of the Constitution and Procedure for the Authority the Director had allowed the complaint about the leaflet in Case AUTH/827/1/99 to proceed as the previous case had not been appealed.

The Panel noted that in the previous case, Case AUTH/802/11/98, an A5 leaflet entitled 'Male Over 50 Prostate Problems?' had been at issue, not an A4 poster. The leaflet in the previous case stated in boxed text 'For a free information leaflet call FREEPHONE [number stated].' This statement did not appear on the leaflet or poster now in question.

The Panel noted that the 'Male Over 50 Prostate Problems?' leaflet and poster encouraged readers who had answered 'yes' to a series of questions about the symptoms of prostate problems to go to see their doctor for help. Both the leaflet and the poster stated 'Most prostate problems can be treated with medicines'. No specific medicine or class of medicine was mentioned. The Panel noted that Clause 20.1 of the Code stated that prescription only medicines (POMs) and certain pharmacy medicines must not be advertised to the general public. Yamanouchi had sponsored the leaflet and poster in question and also marketed Flomax MR (tamsulosin), a POM for the treatment of functional symptoms of benign prostatic hyperplasia. The Panel considered that the leaflet and poster raised public awareness about prostate problems and the fact that they could be treated with medicines; both might facilitate the market development of Flomax MR. The Panel did not consider that either the leaflet or the poster was an advertisement for the product to the general public. No breach of Clause 20.1 was ruled.

The Panel noted the requirements of Clause 20.2 of the Code that information about medicines which was made available to the general public must 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 doctors to prescribe a specific medicine. The Panel accepted that the leaflet and the poster might encourage patients to discuss prostate problems with their doctor but neither encouraged patients to ask their doctor to prescribe a specific medicine. The Panel ruled no breach of Clause 20.2 of the Code.

3 'Waterworks' leaflet

The Panel noted that in the section of the leaflet dealing with BPH a sub-section entitled 'Relaxing the gland with drugs' referred to a number of drugs that could improve BPH symptoms by relaxing the muscle cells within the prostate gland. The leaflet referred to the disadvantages of the earlier medicines which might cause an increase in side effects in people already taking medication to control their hypertension. The leaflet went on to state that 'Fortunately, a new class of drug, the alpha1A-adrenoceptor antagonists, has recently been developed specifically to treat BPH'. The Panel considered that this statement would encourage the reader to ask their doctor about this type of treatment. To the Panel's knowledge, Flomax MR was the only alpha-adrenoceptor antagonist for the treatment of BPH which had been consistently described as an alpha1A-adrenoceptor antagonist. The SPC stated in the mechanism of action section that tamsulosin bound selectively and competitively to postsynaptic alpha1-receptors, in particular to the subtype alpha1A. The SPC also stated that 'No reduction in blood pressure of any clinical significance was observed during studies with Flomax MR' which the Panel understood implied that the product had a high degree of selectivity for the alpha1A-adrenoceptor as opposed to the alpha1B subtype. The Flomax SPC stated that as with other alpha1-blockers a reduction in blood pressure could occur in individual cases during treatment with Flomax MR as a result of which, rarely, syncope could occur.

The Panel noted Yamanouchi's submission that alfuzosin had a relatively greater selectivity for the alpha1A-receptor vs the alpha1B-receptor compared to the older alpha-blockers such as terazosin and prazosin. The SPC for alfuzosin (Xatral) described the product as a selective antagonist of postsynaptic alpha-adrenoceptors. Alpha1A-receptors were not mentioned although it was stated that *in vitro* studies had documented the specificity of alfuzosin for the alpha-adrenoceptors located in the trigone of the urinary bladder, urethra and prostate. The SPC stated that, with regard to interactions with other medicines, antihypertensive agents should be used with caution because of the risk of a hypotensive effect. The Panel considered that this might imply that alfuzosin blocked both alpha1A- and alpha1B-adrenoceptors. Some of the papers provided by Yamanouchi stated that alfuzosin was not selective for any of the alpha1-adrenoceptor subtypes (Abrams *et al* (1995), Chapple *et al* (1996), Buzelin *et al* (1997)).

The Panel did not consider that the 'Waterworks' leaflet was an advertisement to the general public for a prescription only medicine *per se* and ruled no breach of Clause 20.1 of the Code. Nevertheless, in the Panel's view the statement regarding alpha1A – adrenoceptor antagonists would encourage patients to ask their doctors to prescribe such a medicine which in effect would lead to a prescription for Flomax MR. A breach of Clause 20.2 was ruled.

Complaint received **19 January 1999**

Case completed **14 April 1999**

CASE AUTH/830/1/99

GENERAL PRACTITIONER v NOVO NORDISK

Article on Kliovance in Woman magazine

A general practitioner complained about an article which had appeared in Woman magazine. Headed 'what's new', the article stated 'Kliovance, by Novo Nordisk, is the first low-dose, period-free, hormone replacement therapy which controls menopausal symptoms including hot flushes, sweats and headaches, while protecting against brittle bone disease. It eliminates the unwanted side-effects of HRT, such as breakthrough bleeding and breast pain, but contains half the oestrogen and progestogen of other brands. Kliovance is now available on prescription – ask your GP about it.' The complainant alleged that this was blatant advertising. Two patients had brought the article to him.

Complaints about items in the media were judged on the information provided by the pharmaceutical company or its agents to journalists and not on the content of the article itself. The Panel accordingly examined the press pack for Kliovance which consisted of a press release and three 'backgrounders'. The Panel noted that the summary of product characteristics stated that Kliovance (oestradiol/norethisterone) was 'Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in women who are more than one year past the menopause.' No mention was made of the prophylaxis of post-menopausal osteoporosis.

The Panel did not accept that the press materials provided by Novo Nordisk constituted an advertisement for a prescription only medicine to the general public and therefore ruled no breach of the Code in that regard.

The Panel noted that the press release and backgrounder 1 implied that Kliovance could be used to protect against bone loss and backgrounder 2 dealt specifically with the role of norethisterone in the prevention of osteoporosis. In the Panel's view the tone and nature of the press pack meant that it was not factual nor presented in a balanced way. It would encourage patients to ask their doctors to prescribe Kliovance. The Panel therefore ruled a breach of the Code.

A general practitioner complained about an article which had appeared in Woman magazine on 23 November, 1998.

The item was headed 'what's new' and stated 'Kliovance, by Novo Nordisk, is the first low-dose, period-free, hormone replacement therapy which controls menopausal symptoms including hot flushes, sweats and headaches, while protecting against brittle bone disease. It eliminates the unwanted side-effects of HRT, such as breakthrough bleeding and breast pain, but contains half the oestrogen and progestogen of other brands. Kliovance is now available on prescription – ask your GP about it.'

Kliovance contained oestradiol (estradiol) 1mg and norethisterone acetate 500mcg.

COMPLAINT

The complainant stated that the item had been brought to him by two patients. In his opinion it was blatant advertising. Oestradiol 1mg and norethisterone 500mcg were available individually at less than half the cost and in the complainant's opinion the only people to benefit were not the patients but Novo Nordisk shareholders.

When writing to Novo Nordisk Pharmaceuticals Ltd the Authority drew attention to Clauses 20.1 and 20.2 of the Code.

RESPONSE

Novo Nordisk stated that with regard to Clause 20.1 'Medicines must not be advertised to the general public if they are prescription only medicines', Kliovance was a prescription only medicine. The article was not an advertisement produced by Novo Nordisk. The article was a 'news' item produced independently by the magazine; Novo Nordisk had no editorial input and had no prior knowledge of the article.

Novo Nordisk assumed, however, that the article was based on information contained in the consumer press briefing materials prepared by the company. A copy of the consumer press release and associated background notes, together with a list of lay media and freelancers to whom the press materials were sent, was provided. The consumer press briefing materials were approved through Novo Nordisk's promotional material approval system and it therefore accepted full responsibility for them. The press briefing material was mailed to the 'target media' and then followed up by telephone by a public relations agency.

Hormone replacement therapy (HRT) was of interest to many menopausal and post-menopausal women and there had been considerable media discussion of this topic over the last several years. Kliovance was a new HRT with, it was believed, some important advantages in the treatment of the symptoms of oestrogen deficiency in post-menopausal women. Therefore the provision of factual information in the form of a press release was consistent with the requirements of Clause 20.2 of the Code.

In relation to Clause 20.2 and the requirement not to encourage members of the public to ask their doctors to prescribe a specific medicine, the use of the proprietary name in the press release should be commented upon. This was considered acceptable, taking into account that Kliovance was a combination product, ie having two active ingredients (estradiol 1mg, norethisterone acetate 500mcg), which made it difficult to express simply in terms of non-proprietary names.

Estradiol and norethisterone acetate were well-known as active ingredients in HRT preparations of various types and had been used as such for many years, but

dosages of current preparations were based to some extent on their relatively long history of usage. The development programme for Kliovance was specifically designed to investigate the lowest effective dose of estradiol and of norethisterone acetate in their respective uses.

Novo Nordisk submitted that the question of any difference in cost between a formulated combination product and the equivalent dosage contained in tablets with single active ingredients was not a Code issue. It was in the doctor's area of responsibility to prescribe the most appropriate treatment for a particular patient, taking into account both the clinical and non-clinical needs of that patient.

PANEL RULING

The Panel noted that complaints about items in the media were judged on the information provided by the pharmaceutical company, or its agent, to journalists and not on the content of the article itself. It was not necessarily a breach of the Code to include brand names in materials for the press. Conversely the use of non-proprietary names did not necessarily mean that materials were not in breach of the Code.

The Panel examined the consumer press pack which consisted of a press release and three 'backgrounders'. The press release was headed 'Less is more – the arrival of low dose, period-free HRT' and announced the launch of Kliovance. Backgrounder number 1 stated the rationale behind the fixed dose combination of estradiol and norethisterone acetate (NETA) used in Kliovance. Backgrounder number 2 explained the role of NETA in the prevention and treatment of osteoporosis and backgrounder number 3 detailed the tolerability of Kliovance. No details were provided of any telephone follow up by the public relations agency.

The Panel noted that the summary of product characteristics for Kliovance stated that the product was 'Hormone Replacement Therapy (HRT) for estrogen deficiency symptoms in women who are more than one year past the menopause'. There was no indication that the product could be used for the prophylaxis of post-menopausal osteoporosis.

The article in question stated that Kliovance gave protection against brittle bone disease. In the Panel's view brittle bone disease was a lay term for osteoporosis. The Panel noted that the final statement in the consumer press release was 'Kliovance's potential for bone-sparing and protection against osteoporosis has not yet been fully established, although preliminary data looks favourable' and backgrounder 1 explained that NETA was chosen to be included in Kliovance because *inter alia* it was 'the only progestogen shown to increase bone mineral density.' Backgrounder 2 of the press pack specifically dealt with the role of NETA in the prevention of osteoporosis. It was stated that if it were possible to stop post-menopausal bone loss for five years, the overall incidence of hip fracture could be reduced by an estimated 50%. The backgrounder ended with the statement 'Thus, the combination of 17β-estradiol and NETA does appear to be effective in the long-term preventative treatment of postmenopausal bone loss. The data suggests that even at the low doses in continuous combined HRT with Kliovance, there will be a protective effect against bone loss – as well as relieving the vasomotor symptoms associated with the menopause'.

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the general public and medicines which, although not prescription only, might not legally be advertised 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 Panel did not accept that the press materials provided by Novo Nordisk constituted an advertisement for a prescription only medicine to the general public. The Panel therefore ruled no breach of Clause 20.1 of the Code.

The Panel noted that the magazine article ended with 'Kliovance is now available on prescription – ask your GP about it'. The Panel noted that the press release referred to Kliovance as '…an ideal HRT formulation for post menopausal women…'. Backgrounder 1 stated 'For the first time, the introduction of Kliovance allows clinicians to adopt what many would consider to be an ideal HRT management strategy in patients – starting with a low hormone dose tablet, …'. The Panel noted that the press release and backgrounder 1 implied that Kliovance could be used to protect against bone loss and backgrounder 2 dealt specifically with the role of NETA in the prevention of osteoporosis. Kliovance was not licensed for the prophylaxis of post-menopausal osteoporosis. In the Panel's view the tone and nature of the press pack meant that it was not factual nor presented in a balanced way. It would encourage patients to ask their doctors to prescribe Kliovance. The Panel therefore ruled a breach of Clause 20.2.

The Panel noted that the complainant had been concerned that Kliovance cost more than twice the price of its individual components. The Panel did not consider this to be a Code issue. Promotion of a medicine was a legitimate activity for a pharmaceutical company to undertake, regardless of the cost of the medicine, provided that such promotion was in accordance with the Code.

Complaint received **25 January 1999**

Case completed **10 March 1999**

MERCK SHARP & DOHME v SEARLE and PFIZER

Journal advertisement about COX-2 technology

Merck Sharp & Dohme complained about a journal advertisement placed jointly by Searle and Pfizer which was headed 'COX-2 technology: a landmark discovery in molecular biology'. It discussed the two forms of cyclooxgenase, COX-1 and COX-2, and stated that 'Searle and Pfizer are working together to determine the significance of COX-2 specific inhibition and how this new approach may influence the development of treatments for diseases that include an inflammatory component.' Merck Sharp & Dohme alleged that the advertisement was promotion before the grant of the marketing authorization and, furthermore, it was a teaser advertisement. Although Searle's COX-2 inhibitor Celebrex (celecoxib) was not mentioned by name, it left nothing to the imagination and gave notice of Celebrex's imminent launch. Merck Sharp & Dohme alleged that it was part of a pre-marketing campaign by Searle and Pfizer.

The Panel noted that the advertisement only referred to medicines by class. The advertisement stated that the companies were working to determine the clinical significance of COX-2 specific inhibition which was given as 'diseases that include an inflammatory component'. The visual featured in the advertisement was an artist's impression of COX-1, COX-2 and COX-2 specific inhibition which, in the Panel's view, gave no information about a specific medicine or therapy area. No reference, actual or implied, was made to any specific medicine. The Panel considered that the information given in the advertisement was too general to be about any specific medicine. No breach of the Code was ruled in that regard.

The advertisement was not about a medicine. It was a corporate advertisement about an area of research. The Panel considered that given the amount of general information about the research and development of COX-2 inhibition the advertisement was not a 'teaser' as alleged. No breach of the Code was ruled.

Merck Sharp & Dohme Limited submitted a complaint about an advertisement which had appeared in the BMJ, 23 January 1999, and Hospital Doctor, 21 January 1999. The advertisement was headed 'COX-2 technology: a landmark discovery in molecular biology' and had been placed jointly by Searle and Pfizer Limited. The advertisement discussed two forms of cyclooxygenase, COX-1 and COX-2, and concluded by stating that 'Searle and Pfizer are working together to determine the clinical significance of COX-2 specific inhibition and how this new approach may influence the development of treatments for diseases that include an inflammatory component.' The strapline at the bottom of the advertisement stated 'COX-2 specific inhibition. Intelligent medicine with specific direction.'

COMPLAINT

Merck Sharp & Dohme alleged that the advertisement was in breach of Clause 3.1 of the Code as it was promotion prior to the grant of a marketing authorization.

Merck Sharp & Dohme accepted that the advertisement did not mention Searle's COX-2 inhibitor Celebrex (celecoxib) by name but submitted that it left nothing to the imagination and was clearly putting the market on notice of the imminent launch of Celebrex. Furthermore, it was a 'teaser' advertisement in breach of Clause 9.1.

Consideration of the advertisement as a whole clearly showed that it was attempting to position Searle as the owner of the concept of COX-2 specificity. It was the overt reference to COX-2 '…specific inhibition…', together with a description of its mode of action and potential clinical applications, which Merck Sharp & Dohme believed made this advertisement clearly promotion prior to the grant of a marketing authorization.

Merck Sharp & Dohme and Searle each had a COX-2 inhibitor currently awaiting approval for a marketing authorization. At the moment it was unclear which company would have the marketing authorization first. Merck Sharp & Dohme believed that this advertisement formed part of a concerted campaign of pre-marketing by Searle and Pfizer. Its commercial significance could not be under-estimated.

RESPONSE

Responding on behalf of both companies Searle stated that it did not agree that the advertisement promoted the prescription, supply, sale or administration of any medicine and thus believed it did not contravene the Code.

The overall message of the advertisement was clearly science based and general. The text stated that Searle and Pfizer were working 'to determine the clinical significance of COX-2 specific inhibition and how this new approach may influence the development of treatments for diseases that include an inflammatory component'. Whilst reference was made to COX-2 inhibition, there was nothing in this text to indicate, either directly or indirectly, a particular product. Similarly, the only reference to 'potential clinical applications' was 'diseases that include an inflammatory component' and Searle did not believe that this could be interpreted as indicating the potential clinical use of a particular product, or even a class of agents, given that inflammation played some role in such a large, diverse group of diseases. It was worth noting that similar Searle corporate advertising, employing the same visuals and comparable text, had been in use internationally for the last year or so.

Searle submitted that the purpose of the advertisement was to publicize the partnership of Searle and Pfizer in its commitment to research in the area of COX-2 inhibition, following on from the important scientific discovery of the existence of two isoforms of cyclooxygenase.

Searle/Pfizer had identified, as had other companies including Merck Sharp & Dohme, a number of compounds that appeared to be specific inhibitors of COX-2. The therapeutic potential of some of these was currently being evaluated in a number of clinical indications. Much of this information was in the public domain, particularly the recent marketing approval in the USA of one of these compounds, celecoxib.

Searle submitted that there was nothing in the overall presentation or content of the advertisement that constituted promotion of any specific medicine or was designed to elicit an interest in a forthcoming product. The complaint appeared to arise from Merck Sharp & Dohme's belief that the launch of celecoxib in the UK was imminent and that 'the advertisement formed part of a concerted campaign of premarketing' for the product rather than from the content of the advertisement itself. Searle therefore believed it did not contravene either Clause 3.1 or Clause 9.1 of the Code.

Searle provided commercially sensitive details regarding its research in this area.

Searle supplied copies of the information it would supply in response to a general request elicited by these advertisements. If more specific information on clinical areas or products in development was requested a tailored response from its medical information department was provided.

PANEL RULING

The Panel noted that Clause 3.1 of the Code stated that a medicine must not be promoted prior to the grant of the marketing authorization which permitted its sale or supply.

The advertisement in question introduced the concept of COX-2 and discussed Searle and Pfizer's partnership with regard to research in the field of COX-2 specific inhibition. One of the companies' specific COX-2 inhibitors, celecoxib, had been granted marketing approval in the US.

The Panel noted, however, that the advertisement only referred to medicines by class. The advertisement stated that the companies were working to determine the clinical significance of COX-2 specific inhibition which was given as 'diseases that include an inflammatory component'. The visual featured in the advertisement was an artist's impression of COX-1, COX-2 and COX-2 specific inhibition which, in the Panel's view, gave no information about a specific medicine or therapy area. No reference, actual or implied, was made to any specific medicine. The Panel considered that the information given in the advertisement was too general to be about any specific medicine. No breach of Clause 3.1 was ruled.

The Panel noted that the advertisement was not about a medicine. It was a corporate advertisement about an area of research. The Panel considered that given the amount of general information about the research and development of COX-2 inhibition the advertisement was not a 'teaser' as alleged. No breach of Clause 9.1 was ruled.

Complaint received **26 January 1999**

Case completed **22 March 1999**

CASE AUTH/835/1/99

DIRECTOR/PARAGRAPH 16 v SEARLE

Powergel competition

During its consideration of Case AUTH/835/1/99 concerning the activities of a representative, the Panel noted that a box of tissues advertising Powergel (ketoprofen) included a competition which did not appear to be a *bona fide* test of skill. The Panel decided that the matter should be taken up under the provisions of Paragraph 16 of the Constitution and Procedure.

The Panel considered that the Powergel competition was not a *bona fide* test of skill. There were three multiple choice questions. The answers to all the questions were given on the tissue box. The Panel considered that the competition was unacceptable and a breach of the Code was ruled.

During its consideration of Case AUTH/786/11/98 concerning the activities of a representative, the Panel noted that a box of tissues advertising Powergel (ketoprofen) included a competition which did not appear to be a *bona fide* test of skill. The Panel considered that this matter should be taken up with Searle under the provisions of Paragraph 16 of the Constitution and Procedure in relation to the requirements of Clause 18 of the Code.

COMPLAINT

The Panel noted that the supplementary information to Clause 18.2 of the Code referred to competitions and quizzes. Competitions had to be a *bona fide* test of skill and recognise the professional standing of the recipients. The supplementary information referred to the cost of competition prizes. In addition, prizes had to be relevant to the potential recipient's profession or employment. The Panel queried whether the questions on the box of tissues were a *bona fide* test skill.

The Powergel tissue box incorporated a competition which was comprised of three questions:

1 How much does a Powergel 50g tube cost?
a. £4.50 b. £3.25 c. £6.25

2 In terms of NNT, how many patients would you need to treat with ketoprofen gel to achieve a successful outcome?
a. 6.7 b. 3.5 c. 2.6

3 What percentage of patients had a successful outcome after treatment with topical NSAID containing ketoprofen?
a. 66.2% b. 70.9% c. 76.1%

RESPONSE

Searle stated that each representative had been supplied with 200 tissue boxes to leave with customers. The competition had a total of five prize winners for the first five correct answers 'out of the hat'. The prize was a Samsonite brief case (cost £85).

Searle stated that it was awaiting any final entries (closing date 29/01/99) before contacting the winners. The representatives were no longer detailing with this item and any remaining stocks of the tissue box would be destroyed.

Searle submitted that the competition was a *bona fide* test of skill requiring the participant to read the information provided on the box and refer to the review in the British Medical Journal which was the subject of the competition. However, the company appreciated that this had been raised as a matter of concern and would ensure that future competitions were more closely scrutinised and would take all possible steps to avoid any potential breach of Clause 18.2 of the Code.

PANEL RULING

The Panel noted that the supplementary information to Clause 18.2 (Competitions and Quizzes) stated that any competition must be a *bona fide* test of skill and must recognise the professional standing of the recipient.

The Panel considered that the Powergel competition was not a *bona fide* test of skill. There were three multiple choice questions. The answers to all the questions were given on the tissue box. The Panel considered that the competition was unacceptable. It was not possible to breach Clause 18.2 which gave an exemption to the requirements of Clause 18.1. The Panel therefore ruled a breach of Clause 18.1 of the Code.

Proceedings commenced 12 January 1999

Case completed 10 February 1999

GENERAL PRACTITIONER v GLAXO WELLCOME

Meeting in Dublin

A general practitioner complained about an invitation which he had received to attend a meeting in Dublin organised by Allen and Hanburys which was entitled 'UK and NI/Ireland Conference on Developments in Asthma Management'. He considered this totally irresponsible at a time when the NHS was so short of funds. Such meetings could easily be held locally and should have a strictly balanced protocol driven by cost effective prescribing and not company profits. An earlier Allen & Hanburys meeting in Dublin had been ruled in breach of the Code.

The Panel considered that this meeting differed from the earlier one as the latter had involved a meeting in Dublin where the delegates and most of the speakers had come from three regions in the UK, the west midlands, Wessex and the south west of England. Those attending the meeting now under consideration included a significant proportion from Ireland itself. The Panel did not consider it unreasonable in principle for UK pharmaceutical companies to hold meetings in the Republic of Ireland which were attended by UK doctors provided there were valid and cogent reasons for so doing. The content had to apply to both countries, a reasonable proportion of participants from each country should attend, the costs and logistics should be reasonable and the meeting should be consistent with the requirements of the Code as to educational content and the balance between that and the hospitality provided.

On the one hand the Panel considered that the cost of the meeting was high and might exceed the level which some recipients would normally adopt when paying for themselves. On the other hand the meeting was a joint meeting for doctors from the UK and Ireland. Given the nature of the meeting, the Panel considered that although the costs were on the limits of acceptability they were not inappropriate. The content was appropriate to both the UK and Ireland and a reasonable proportion of participants had been invited from Ireland. On balance the Panel considered that the meeting was an acceptable one, both as to the educational content and associated hospitality. No breach of the Code was ruled.

A general practitioner complained about an invitation which he had received to a meeting in Dublin organised by Allen & Hanburys. The meeting, entitled 'UK and NI/Ireland Conference on Developments in Asthma Management', was to take place at Jurys Hotel, Dublin, on 12-14 March 1999.

COMPLAINT

The complainant said that it would be recalled that two years ago Glaxo Wellcome UK Limited had been found to be in breach of the Code for holding an Allen & Hanburys meeting in Dublin which could more easily and considerably more cheaply have been held in the south west of England. It was, the complainant believed, fined approximately £4,000.

The fine, compared with the company's annual profits, was similar to a multi-millionaire getting a £20 parking ticket, in which repeated offences also occurred. Unfortunately for Allen and Hanburys the complainant had received an invitation to another similar meeting, again in Dublin, again at a cost greater than £1,000 per delegate, and again unnecessary.

At a time when the NHS was so short of funds it seemed to the complainant totally irresponsible behaviour. Such meetings could easily be held locally.

The complainant ventured to suggest that in general it would be beneficial to the Health Service if pharmaceutical company representatives – many of them ex-nurses – returned to clinical medicine where they were desperately needed. The money spent by the industry in promotion should be spent only on meetings with a strict balanced protocol which was driven by cost effective prescribing, not company profits.

The Authority drew Glaxo Wellcome's attention to Clauses 19, 9.1, 2 and 21 of the Code.

In its reply to the complainant, the Authority pointed out in relation to the earlier case that there was no system of fines. The administrative charges made were contributions to the running costs of the Authority, which was self supporting.

RESPONSE

Glaxo Wellcome said that the complainant rightly drew attention to the decision, upheld on appeal, against Glaxo Wellcome in late 1997 in Case AUTH/632/10/97. The company's aim was to set, and be seen to set, the highest standard of ethical conduct for its meetings. It accepted the ruling and, in the light of that, issued very clear guidance on the setting up and running of such meetings. The guidance was sent to all members of Glaxo Wellcome UK sales force, marketing managers and medical advisers. A copy was provided.

Bearing this ruling in mind, in 1998 Glaxo Wellcome held a successful series of meetings which were of high educational and scientific content, received postgraduate education allowance (PGEA) approval and indeed were inspected by those responsible for monitoring such educational meetings. Their comments had been considered and incorporated into the planning for this meeting. Copy letters were provided.

The Chairman of the Board of Glaxo Wellcome Ireland was also Chairman of the UK Board and had responsibility for both countries. Two other members of the UK Board, the Human Resources Director and the Medical Director, also provided services to Ireland. Thus sponsorship of a joint meeting of Irish and UK doctors would seem reasonable.

This meeting was an international primary care meeting to which 35 Irish doctors had been invited (representing 1.4% of GPs in Eire), with between 120 and 130 doctors from all parts of the UK (roughly 0.4% of UK GPs). It would be noted from the draft programme that both the chairman and several of the key speakers were from Ireland.

The programme and indeed the overall theme for this forum on the evolution in asthma management was discussed extensively with the speakers and informally with many other leading UK physicians in primary care who had an interest and expertise in managing asthma. Indeed a mission statement from these GPs was used internally to capture Glaxo Wellcome's objective: 'The transfer of best practice in asthma management throughout the UK and Eire'. Many of those with whom the company discussed the programme considered that the best way of facilitating the information transfer would be to spend protected time with colleagues. This format had been well used in the past with considerable approval from the delegates. PGEA approval was anticipated for this particular meeting.

The complainant asserted that the cost of this meeting was greater than £1,000 per delegate and again unnecessary. The average cost per delegate for travel, hotel accommodation and catering came to £553.02 and it would be noted that the company had opted to hold these meetings at Jurys Hotel in Dublin rather than the Shelbourne, which was commented on in the previous ruling as being the most expensive hotel in Dublin. For comparison, the average cost per delegate to hold the meeting in the Swallow Hotel, Bristol, considered to be of similar standard, would be £567 per delegate. Correspondence relating to this was provided.

The invitation provided by the complainant highlighted the fact that it was an international meeting, a conference looking at developments in asthma management, with the venue being of secondary importance.

The number of suitable venues in the UK to host such a meeting, with an attendance of 200 or so, including Allen & Hanburys' staff, with conference facilities, was very small. They therefore tended to be booked many months in advance. One of the few other mainland venues which could cater for such numbers was the Belfry Hotel in the midlands. Glaxo Wellcome was already holding a parallel international meeting at the Belfry on the same date, with a large number of customers from hospitals and primary care in England, Ireland, Scotland and Wales invited. This meeting was planned for over 280 delegates, of whom 15 or so would be flown over from Ireland. Arranging the two meetings at these venues would involve approximately 135 flights to or from Ireland, whereas if the GP meeting had been held in mainland UK and the Belfry meeting in Ireland, 300 return flights would have been necessary.

With regard to the value of holding such a meeting, Glaxo Wellcome had on file many letters of commendation from previous delegates to such meetings, testifying to the enormous educational value and acceptability of both the tone and content of the meetings. The company had striven very hard to provide balanced meetings, albeit with some promotional content in specific sections. The education on offer was over and above that provided by the NHS and was highly valued by Glaxo Wellcome's customers. The programme for this meeting, which was sent out to those who indicated an interest, quite clearly identified the promotional element that was confined to the Saturday afternoon. This was in contrast to the overriding, non-promotional, educational messages that would be delivered throughout the Saturday morning and again throughout the Sunday morning. Indeed this one promotional session very much addressed the cost effective prescribing that the complainant suggested should be tested in his complaint.

Glaxo Wellcome was a research based organisation with a strong commitment to supporting the development of novel therapies, particularly in respiratory medicine, and working with its customers to aid academic research, the highest clinical standards within the NHS, educational and service support for primary care within the UK.

Moving on to consideration of Clauses 2, 9.1 and 19.1 of the Code: Glaxo Wellcome believed the whole concept of this meeting and of the others in the series was to provide meetings of interest and the highest educational content developed in liaison with the speakers and chairmen and guided significantly by the top respiratory interested primary care physicians in the country. Glaxo Wellcome believed that it had shown a very clear undertaking to abide by the Code both in spirit and letter and with its revised guidelines following the complaint upheld in late 1997. Glaxo Wellcome therefore felt that the arguments above demonstrated that it was not in breach of the Code.

In summary Glaxo Wellcome did not accept that it was in breach of Clauses 2, 9.1, 19.1 or 21 of the Code and maintained that the meeting was a truly international meeting with delegates invited from a large area of Britain and Ireland. The presence of chairmen and speakers from both countries reinforced this. Glaxo Wellcome was providing an appropriate level of hospitality for a highly scientific and educational meeting that had attracted much interest. It believed that this conformed to the highest ethical standards within the British pharmaceutical industry.

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 Panel noted that the Code did not prevent companies from holding meetings for UK health professionals at venues outside the UK. There had to be valid and cogent reasons for so doing. When considering whether a meeting and associated

hospitality contravened the Code all the circumstances had to be considered including cost, location, educational content, level of hospitality and the overall impression created by the arrangements. Each case had to be considered on its own merits. In the Panel's view the programme should attract delegates and not the venue.

The Panel noted that the invitation to the meeting provided by the complainant did not include much detail about the programme for the meeting. The invitation stated that the meeting was an international clinical conference for health professionals with an interest in respiratory conditions and that the conference would provide an update and examine the perspectives of primary care doctors concerning asthma management and medication. The invitation stated that once details of the programme had been finalised full information would be forwarded.

The Panel noted that the educational content of the meeting ran from 9.30 until 15.45 on the Saturday and from 9.30 until 12.45 on the Sunday followed by return travel. The Panel considered that the educational content was not unreasonable. Glaxo Wellcome had invited 35 Irish doctors and between 120 and 130 doctors from all parts of the UK. One of the speakers and one of the two chairmen were from Ireland.

The Panel noted that the average cost per delegate was £553.02. This included travel, hotel accommodation and catering. The Panel noted the submission from Glaxo Wellcome that the average cost of holding the meeting at a comparable venue in the UK would be £567 per delegate.

The Panel considered that this meeting differed from that which was the subject of Case AUTH/632/10/97 as the latter had involved a meeting in Dublin where the delegates and most of the speakers had come from three regions in the UK, the west midlands, Wessex and the south west of England. The Appeal Board had considered that it could have been held at a convenient location in England as this would not necessarily have increased the overall travelling time. A breach of Clause 19.1 of the Code had been ruled. Those attending the meeting now under consideration included a significant proportion from Ireland itself.

The Panel did not consider it unreasonable in principle for UK pharmaceutical companies to hold meetings in the Republic of Ireland attended by UK doctors provided there were valid and cogent reasons for so doing. The content had to apply to both countries, a reasonable proportion of participants from each country should attend, the costs and logistics should be reasonable and the meeting should be consistent with the requirements of the Code as to educational content and the balance between that and the hospitality provided. The Panel noted that a working party had been established by the Code of Practice Appeal Board and the ABPI Board of Management to review the question of meetings and hospitality.

The Panel considered that on the one hand the cost of the meeting at £553.02 per delegate was high. The Panel accepted that this might exceed the level which some recipients would normally adopt when paying for themselves. On the other hand the meeting was a joint meeting for doctors from the UK and the Republic of Ireland. Given the nature of the meeting, the Panel considered that although the costs were on the limits of acceptability they were not inappropriate. The Panel noted that content was appropriate to both the UK and Ireland and a reasonable proportion of participants had been invited from Ireland. On balance the Panel considered that the meeting was an acceptable one, both as to the educational content and the associated hospitality. The Panel ruled that there had been no breach of Clause 19.1 of the Code. It thus followed that there was no breach of Clauses 2, 9.1 and 21 of the Code.

Complaint received **11 February 1999**

Case completed **8 April 1999**

GENERAL PRACTITIONER v YAMANOUCHI PHARMA

Men's Health Matters – public awareness leaflet

A general practitioner complained about a leaflet entitled 'Male Over 50 Prostate Problems?' which gave the symptoms of prostate problems and stated that most could be treated with medicines and that your doctor would be able to help. The complainant said that the leaflet had been distributed to all households locally via a free newspaper. The complainant had traced the leaflet as emanating from Men's Health Matters and funded by Yamanouchi Pharma, the makers of Flomax MR (tamsulosin). Although the company would say that it was merely raising awareness, the complainant considered it was anticipating an increase in sales of its product as a proportion of the increased prescribing.

The Authority informed the complainant that a complaint about a similar leaflet had been considered previously and no breach of the Code had been ruled (Case AUTH/802/11/98). There had been no appeal in that case and, as provided for in the Constitution and Procedure, the new complaint was allowed to proceed. Either party, as appropriate, would be able to appeal the Panel's ruling.

In Case AUTH/802/11/98, the Panel had considered that the leaflet raised public awareness about prostate problems and the fact that they could be treated with medicines. Although the leaflet might facilitate the market development of Flomax MR, the Panel did not consider that the leaflet was an advertisement for the product to the general public. The leaflet might encourage patients to discuss prostate problems with their doctor but it did not encourage them to ask their doctor to prescribe a specific medicine. No breach of the Code was ruled. The Panel considered that this ruling also applied to the new complaint, a decision which was not appealed.

A general practitioner complained about a leaflet which had the title 'Male Over 50 Prostate Problems?' The leaflet, in a series of questions to the reader, gave the symptoms of prostate problems and stated "No, it isn't 'your age', and something simple can be done about it. Most prostate problems can be treated with medicines. Your doctor will be able to help. Ring the surgery NOW to make an appointment". At the bottom of the leaflet was a logo, MHM, and 'Men's Health Matters'.

The Authority informed the complainant that a complaint about a similar leaflet had been considered previously and no breach of the Code had been ruled (Case AUTH/802/11/98). Paragraph 5.1 of the Constitution and Procedure for the Authority said that the Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Code of Practice Panel which had not been the subject of an appeal to the Code of Practice Appeal Board. The complainant was told that the Director had decided that, as there had been no appeal in Case AUTH/802/11/98, the complaint would proceed with the Panel making a ruling in the first instance as usual. Following that, either party could appeal the decision to the Appeal Board.

COMPLAINT

The complainant stated that the leaflet had been distributed to all households locally via the local free newspaper. He objected to the nature of the leaflet. Although the company would clearly say that it was merely raising awareness of the problem, it was anticipating an increase in sales of its product as a proportion of the increased prescribing. The complainant had traced the leaflet as emanating from Men's Health Matters and being funded by Yamanouchi Pharma, the makers of Flomax.

RESPONSE

Yamanouchi Pharma Ltd said the leaflet was enclosed with local newspapers which were then distributed to the public in the UK.

The purpose of the leaflet was educational, aiming to improve the general public's awareness of prostate diseases as symptoms might severely impair their quality of life and it encouraged males with problems to seek medical attention. A recent Gallup survey conducted in the UK had shown that the majority of men with health issues did not seek medical attention despite having symptoms because they were either too embarrassed to visit their family doctor or they felt that associated symptoms were part of the normal ageing process. A copy of the survey was provided.

In 1997 Yamanouchi initiated a health education programme concerning the prostate under the umbrella of Men's Health Matters.

Yamanouchi took all complaints against its activities seriously and consequently reviewed this leaflet again. However, it remained satisfied that the leaflet was not in breach of the Code, and specifically not in breach of Clause 20, as it did not promote any product but merely provided information on a therapeutic area. Provision of information on a therapeutic area was not against the Code. This was also the Panel's view in its adjudication of a previous complaint.

Yamanouchi pointed out that it had received encouraging responses from patient support groups active in educating the public about prostate problems. A letter from one such group was provided.

PANEL RULING

The Panel noted its ruling in the previous case, Case AUTH/802/11/98.

Previous ruling in Case AUTH/802/11/98 The Panel noted that the leaflet 'Male Over 50 Prostate Problems?' encouraged readers who had answered 'yes' to the series of questions about the symptoms of prostate problems, to go to see their doctor for help. The leaflet stated 'Most prostate problems can be

treated with medicines'. No specific medicine or class of medicine was mentioned on the leaflet. There was no other reference to medicines in the leaflet. The Panel noted that Clause 20.1 of the Code stated that prescription only medicines (POMs) and certain pharmacy medicines must not be advertised to the general public. Yamanouchi had sponsored the leaflets in question and also marketed Flomax MR (tamsulosin) a POM for the treatment of functional symptoms of benign prostatic hyperplasia. The Panel considered that the leaflet raised awareness about prostate problems and the fact that they could be treated with medicines. The leaflet might facilitate the market development of Flomax MR. The Panel did not consider that the leaflet was an advertisement for the product to the general public. No breach of Clause 20.1 was ruled.

The Panel noted the requirements of Clause 20.2 of the Code that information about medicines which was made available to the general public must 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 doctors to prescribe a specific medicine. The Panel accepted that the leaflet might encourage patients to discuss prostate problems with their doctor but the leaflet in question did not encourage patients to ask their doctor to prescribe a specific medicine. The Panel ruled no breach of Clause 20.2 of the Code.

Panel ruling in Case AUTH/841/2/99 The Panel considered its ruling in Case AUTH/802/11/98 would also apply to the new complaint. The Panel, therefore, ruled no breach of Clauses 20.1 and 20.2 of the Code. This decision was not appealed.

Complaint received **15 February 1999**

Case completed **14 March 1999**

CODE OF PRACTICE REVIEW – MAY 1999

Cases in which a breach of the Code was ruled are indexed in **bold type**.

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827/1/99	**Health Authority Primary Care Medical Adviser v Yamanouchi Pharma**	**Men's Health Matters – public awareness campaign**	**Breach Clause 20.2**	**No appeal**	**Page 54**
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833/1/99 & 834/1/99	Merck Sharp & Dohme v Searle and Pfizer	Journal advertisement about COX-2 technology	No breach	No appeal	Page 60
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840/2/99	General Practitioner v Glaxo Wellcome	Meeting in Dublin	No breach	No appeal	Page 63
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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, more than 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 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 in connection therewith
- the provision of information to the general public either directly or indirectly
- 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 Philip Cox 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 0171-930 9677 facsimile 0171-930 4554).

SUPPLEMENT TO THE CODE OF PRACTICE REVIEW MAY 1999

APPROVED INFORMATION ON THE INTERNET

- **the public assessment report**
- **the package leaflet**
- **the summary of product characteristics**

The Authority has received a number of enquiries about recent reports of a decision made by the EU Pharmaceutical Committee that pharmaceutical companies can publish approved information on open access sites on the Internet without infringing the EC Directive on the advertising of medicinal products for human use. It may be of assistance to companies to clarify the position.

The Code of Practice for the Pharmaceutical Industry permits companies to supply copies of the summary of product characteristics and the package leaflet to members of the public on request. This is specifically referred to in the supplementary information to Clause 20.2. Companies can also put faithful reproductions of these documents on open access sites on the Internet as stated in the guidance on the Internet issued by the Authority in May 1996 (copies of which are available on request).

The Pharmaceutical Committee's interpretative guidance states:

"The unmodified and unabridged publication on the Internet of information on medicinal products (prescription only and OTC products) which has been authorised by competent authorities, eg:
- the Summary of Product Characteristics of a medicinal product
- the package leaflet of a medicinal product
- public assessment reports of a medicinal product

should normally not be considered as advertising, unless the presentation of this information clearly constitutes a "hidden inducement" to promote the prescription, supply, sale or consumption of the medicinal product. The existence/non-existence of a "hidden inducement" must be checked on a case-by-case basis, taking into account the overall presentation of the information.

The above principle applies equally to the publication of compendia of Summary of Product Characteristics, package leaflets or public assessment reports in printed form."

Although this is consistent with current UK practice, it will represent a significant change in those European countries that have until now considered such information to be advertising.

The references to summaries of product characteristics and package leaflets in the supplementary information to Clause 20.2 of the Code of Practice and in the Authority's Internet guidance should be regarded as applying also to public assessment reports.

May 1999