PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 37 AUGUST 2002

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.

Annual Report for 2001

The Annual Report of the Prescription Medicines Code of Practice Authority for 2001 has now been published and copies have been sent to all who are on the mailing list for the Code of Practice Review. Further copies are available on request.

As previously reported in the Review, there were 138 complaints in 2001 as compared with 121 in 2000, an increase of about 14%. There were 127 complaints in 1999.

The 138 complaints in 2001 gave rise to 147 cases as compared to 134 in 2000. The reason that the number of cases usually differs from the number of complaints is because some complaints involve more than one respondent company and because some complaints do not become cases at all, usually because no *prima facie* case is established.

A notable feature in 2001 was that while the number of complaints increased by 14%, the number of individual allegations made rose by over 36%, there being 478 in 2001 as compared with 350 in 2000. This resulted from complex multi-issue complaints received from pharmaceutical companies. The number of complaints made by pharmaceutical companies in 2001 exceeded the number made by health professionals, there being 60 from companies and 56 from health professionals. It is usually the case that the number of complaints made by health professionals exceeds the number made by pharmaceutical companies, though that was not the case in 1996 and 1999, and now again in 2001.

Of the 478 rulings made by the Code of Practice Panel, 422 (88.3%) were accepted by the parties, 34 (7.1%) were unsuccessfully appealed and 22 (4.6%) were successfully appealed. This compares with the 6.6% of rulings which were successfully appealed in 2000.

The Code of Practice Panel met 92 times in 2001 (86 in 2000) and the Code of Practice Appeal Board met 11 times in 2001 (9 in 2000). The Appeal Board considered appeals in 32 cases as compared with 35 in 2000.

Withdrawal of complaints

The Authority occasionally receives requests that a complaint be withdrawn or an appeal discontinued.

It should be noted that the Authority's Constitution and Procedure provides that a complaint may be withdrawn by a complainant, with the consent of the respondent company, up until such time as the latter's comments on the complaint have been received by the Authority, but not thereafter.

An appeal may be withdrawn by a complainant, with the consent of the respondent company, up until such time as the latter's comments on the reasons for the appeal have been received by the Authority, but not thereafter. An appeal by a respondent company may be withdrawn at any time, but if notice is given after the papers have been circulated to the Code of Practice Appeal Board then the higher administrative charge will be payable.

Public reprimand for Schering-Plough

Schering-Plough Ltd has been publicly reprimanded by the ABPI Board of Management which noted the number of cases involving NeoClarityn and the similarity between the complaints.

Schering-Plough had been required by the Code of Practice Appeal Board to submit to an audit by the Prescription Medicines Code of Practice Authority in relation to another case, Case AUTH/1210/7/01. In its consideration of Case AUTH/1234/10/01, the ABPI Board had sight of the report for the audit in the previous case.

Full details can be found at page 3 in this issue of the Review in the report for Case AUTH/1234/10/01.

New Authority staff member

Mr Peter Clift has been appointed to the staff of the Authority and will be particularly concerned with administrative support to the Code of Practice Appeal Board.

Peter, who joined the Authority at the beginning of May, has a first degree in cell and molecular biology and a Master's degree following research in immunology. Prior to joining the Authority, he was at the Hammersmith Hospital.

The Authority welcomes Peter to its staff and believes that he will make a valuable contribution to its work.

CODE OF PRACTICE TRAINING

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

These seminars comprise a full day course offering lectures on the Code and the procedures under which complaints are considered, discussion 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:

Wednesday, 27 November

Monday, 16 December

Tuesday, 21 January

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

For further information regarding any of the above, please contact Jean Rollingson for details (020 7930 9677 extn 1443).

How to contact the Authority

Our address is:

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

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Lisa Matthews (020 7930 9677 extn 1473).

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

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

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

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

CASE AUTH/1234/10/01

SCHWARZ PHARMA v SCHERING-PLOUGH

NeoClarityn mailing

Schwarz Pharma complained about a 'Dear Doctor' letter headed 'Discontinuation of Clarityn (loratadine 10mg) Tablets – 3 Months Notice' issued by Schering-Plough.

Schwarz alleged that the claim '… for the past 50 years Schering-Plough has striven to bring improved anti allergic medicine to the NHS. Our latest development in this field is NeoClarityn, desloratadine, a purified development of Clarityn' implied that NeoClarityn was an improved version of Clarityn, but did not explain in what way. The European Public Assessment Report for NeoClarityn concluded that there was no difference in efficacy between the two treatments.

The Panel considered the claim was misleading as alleged and breaches of the Code were ruled. These rulings were appealed. The Appeal Board noted that each party had misquoted the claim 'Our latest treatment in this field is NeoClarityn, desloratadine, a purified development of Clarityn …' replacing 'treatment' with 'development'. The error had been repeated by the Panel as part of its ruling. The Appeal Board considered that the claim and the letter gave the impression that NeoClarityn was an improved medicine compared to Clarityn and there was no evidence that this was so. The Appeal Board considered that the claim was misleading and not capable of substantiation as alleged. The Appeal Board upheld the Panel's rulings of breaches of the Code.

Schwarz noted that, unlike Clarityn, NeoClarityn had no licence for perennial allergic rhinitis, therefore patients would need to be prescribed another antihistamine of unknown cost. The company thus alleged that the claim that NeoClarityn '… is exactly the same price as Clarityn, and will therefore not have an impact on your prescribing budget' was misleading.

The Panel considered that given the similarity in name between Clarityn and NeoClarityn there was potential for confusion. Insufficient effort had been made to distinguish between the two products; not all patients on Clarityn could be transferred onto NeoClarityn and the prescribing budget referred to related only to those patients with seasonal allergic rhinitis and/or chronic idiopathic urticaria. The Panel considered that the claim implied that the whole of the Clarityn prescribing budget would stay the same when the product was withdrawn and replaced by NeoClarityn; this was not so. A breach of the Code was ruled. This ruling was appealed. The Appeal Board considered that it had not been made sufficiently clear that not all patients on Clarityn could be transferred to NeoClarityn. The claim implied that the change would have no impact on the prescribing budget which was not so. The Appeal Board upheld the Panel's ruling of a breach of the Code.

The Appeal Board noted the previous cases concerning the promotion of NeoClarityn by Schering-Plough. In Case AUTH/1210/7/01, which concerned a breach of undertaking, Schering-Plough had been required to undergo an audit of its procedures in relation to the Code. That audit had taken place in October 2001. When considering the audit report the Appeal Board had noted the action taken by Schering-Plough and that it had not implemented some of the recommendations from the previous audit in October 1998. The Appeal Board did not consider that the circumstances warranted reporting Schering-Plough to the ABPI Board of Management. The Appeal Board had decided that Schering-Plough should undergo another audit in six months (May 2002) to check that the recommendations of the recent audit had been implemented. On this basis the Appeal Board had decided that no further action was necessary.

The Appeal Board noted that the letter at issue in the present case had been distributed prior to the October 2001 audit. Schering-Plough had subsequently appealed the Panel's rulings in the present case. The Appeal Board was very concerned about Schering-Plough's promotion of NeoClarityn. There had been a number of cases and the company had repeatedly been ruled in breach of the Code for similar issues, albeit not exactly the same. One case had however involved a breach of undertaking. The Appeal Board considered that the circumstances warranted reporting the company to the ABPI Board of Management pursuant to Paragraph 12.1 of the Constitution and Procedure for it to decide whether further sanctions should be applied.

The ABPI Board of Management was very concerned about the conduct of Schering-Plough. The number of cases involving NeoClarityn and the similarity between the complaints were noted. The ABPI Board noted that Schering-Plough had been audited twice by the Authority and a further audit was to take place in May 2002. The ABPI Board requested sight of the May 2002 audit report.

As this was a serious matter the ABPI Board decided that Schering-Plough should be reprimanded and details of that reprimand published.

On receipt of the audit report, the ABPI Board decided that no further action was necessary.

Schwarz Pharma Limited complained about a 'Dear Doctor' letter (ref NCL/01-136) headed 'Discontinuation of Clarityn (loratadine 10mg) Tablets – 3 Months Notice' issued by Schering-Plough Limited and signed by its Managing Director.

COMPLAINT

Schwarz stated that Schering-Plough had recently written to GPs and pharmacists to inform them of the discontinuation of Clarityn 30 tablet packs 'for commercial reasons'. Schwarz regarded this mailing as promotional material for NeoClarityn (desloratadine) and not commercial information for the following reasons: it made promotional claims about NeoClarityn; NeoClarityn prescribing

information was included and it had a promotional item identification number (NCL/01-136&7).

Schwarz alleged that the claim '… for the past 50 years Schering-Plough has striven to bring improved anti allergic medicine to the NHS. Our latest development in this field is NeoClarityn, desloratadine, a purified development of Clarityn' implied that NeoClarityn was an improved version of Clarityn, but did not explain in what way it was superior. There was no reference made to evidence supporting this claim and Schwarz understood that there had been no *in vivo* clinical trials comparing these two products. Additionally, the European Public Assessment Report (EPAR) for NeoClarityn concluded that there was no difference in efficacy between the two treatments. Breaches of Clauses 7.2 and 7.4 were alleged.

Schwarz also alleged that the claim that NeoClarityn '… is exactly the same price as Clarityn, and will therefore not have an impact on your prescribing budget' was misleading. Unlike Clarityn, NeoClarityn had no licence for perennial allergic rhinitis. Not all patients prescribed Clarityn could be prescribed NeoClarityn. Clarityn would no longer be available for perennial allergic rhinitis and patients would need to be prescribed another antihistamine of unknown cost. This meant that the prescribing budgets could not be legitimately compared. A breach of Clause 7.3 was alleged.

These two claims together with the withdrawal of Clarityn constituted an implication that NeoClarityn was the same as Clarityn, only better. Schering-Plough had previously been ruled in breach of the Code for this in multiple complaints against it (eg Case AUTH/1172/3/01) under Clause 7.

Schwarz stated that this was the latest in a series of breaches of the Code involving Schering-Plough's promotion of NeoClarityn. In the August 2001 Code of Practice Review there were over 40 breaches of the Code, in four different complaints, in the promotional material for NeoClarityn. Schwarz once again questioned the procedures in place that would allow such material to be certified for release, particularly after the previous complaints. Schwarz had lost all confidence in Schering-Plough's ability to self-regulate its compliance with the Code. For this reason, it would like to formally request that a report was made to the Appeal Board with a suggestion that Schering-Plough be audited.

Schwarz requested reassurance that all of Schering-Plough's materials had been amended to comply with previous undertakings and in particular its representative training materials (to which Schwarz did not have access) examined to ensure that appropriate changes had been made in accordance with those undertakings.

RESPONSE

With regard to the claim '… for the past 50 years, Schering-Plough has striven to bring improved anti-allergic medicines to the NHS. Our latest development in this field is NeoClarityn, desloratadine, a purified development of Clarityn', Schering-Plough stated that it could not agree with Schwarz's argument. NeoClarityn was a purified development of Clarityn. It made no suggestion as to whether it was superior, inferior or equivalent. 'Development' was simply used in the dictionary meaning of 'a fact, event or happening'. Again Schering-Plough made no claim as to whether it was a good, bad or indifferent development. That Schering-Plough strived to bring improved medicines to the NHS was axiomatic. It did not infer that it was always successful as a result of its striving.

The second claim at issue '… is exactly the same price as Clarityn and therefore will not have an impact on your prescribing budget' appeared to concern Schwarz because 'Unlike Clarityn, NeoClarityn has no licence for PAR'. Schering-Plough pointed out that the quotation was selective; the full sentence read 'This new treatment for your patients with seasonal allergic rhinitis and chronic idiopathic urticaria is exactly the same price as Clarityn and therefore will not have an impact on your prescribing budget'. It was made clear that this change only affected patients with seasonal allergic rhinitis and chronic idiopathic urticaria. For these patients a switch from Clarityn to NeoClarityn, should a doctor wish to make such a switch, was cost neutral. No mention was made of switches of patients with PAR.

Schwarz commented that 'These two claims together with the withdrawal of Clarityn constitute an implication that NeoClarityn is the same as Clarityn only better'. Schering-Plough pointed out that neither was implied nor stated. The letter was a factual one, and made it clear that the discontinuation was for commercial reasons. Nowhere did it state that the withdrawal was related to clinical claims.

Schering-Plough believed it acted in good faith to inform health professionals about a development that would perforce impact on their prescribing habits and strongly disagreed that the letter was misleading.

PANEL RULING

The letter at issue began by stating that, *inter alia*, '… for the past 50 years Schering-Plough has striven to bring improved anti allergic medicine to the NHS'. This was immediately followed by the second paragraph which started with 'Our latest treatment in this field is NeoClarityn, desloratadine, a purified development of Clarityn'. The Panel considered that readers would reasonably assume from the first two paragraphs that, compared with Clarityn, NeoClarityn was an improved anti allergic medicine produced by Schering-Plough. This impression was, in the Panel's view, compounded by the description of NeoClarityn as the 'latest treatment in this field', 'a purified development of Clarityn' and a subsequent statement that 'as a result of this development, Clarityn will be discontinued …'. The Panel noted Schering-Plough's comments on the definition of 'development' but further noted that the New Shorter Oxford English Dictionary (1993) defined development, *inter alia*, as 'evolution', 'growth, a developed form or product', 'a stage of advancement'.

The Panel noted that there were no *in vivo* clinical trials comparing Clarityn and NeoClarityn and

Schwarz's submission that the EPAR concluded that there was no difference in efficacy between the two products.

The Panel considered that the claim '… for the past 50 years Schering-Plough has striven to bring improved anti allergic medicine to the NHS. Our latest development in this field is NeoClarityn, desloratadine, a purified development of Clarityn' implied that NeoClarityn was an improved version of Clarityn as alleged and on the evidence before it that was not so. The Panel considered the claim misleading as alleged. Breaches of Clauses 7.2 and 7.4 were ruled.

With regard to the second claim at issue 'This new treatment for your patients with seasonal allergic rhinitis and chronic idiopathic urticaria is exactly the same price as Clarityn and will therefore not have an impact on your prescribing budget', the Panel noted that according to the summary of product characteristics NeoClarityn was indicated for seasonal allergic rhinitis and chronic idiopathic urticaria. Clarityn was indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis and for those associated with idiopathic chronic urticaria. The licensed indications for NeoClarityn were thus more restrictive than for Clarityn. The Panel considered that given the similarity in name between Clarityn and NeoClarityn there was potential for confusion. Whilst the licensed indications for NeoClarityn had been stated the Panel considered that insufficient effort had been made to distinguish between the two products; it had not been made sufficiently clear that not all patients on Clarityn could be transferred onto NeoClarityn and that the prescribing budget referred to related only to those patients with seasonal allergic rhinitis and/or chronic idiopathic urticaria. Patients on Clarityn with perennial allergic rhinitis would have to be prescribed another antihistamine of unknown cost. On balance the Panel considered that the claim implied that the whole of the Clarityn prescribing budget would stay the same when the product was withdrawn and replaced by NeoClarityn; this was not so. The Panel noted that a breach of Clause 7.3 had been alleged; a breach of that clause was ruled.

The Panel noted Schwarz's comments about previous cases regarding the promotion of NeoClarityn by Schering-Plough and its request that a formal report be made to the Appeal Board with a suggestion that Schering-Plough be audited. The Panel noted that Paragraph 8 of the Constitution and Procedure stated that the Panel should report a company to the Appeal Board if it failed to comply with the procedures or if its conduct warranted consideration by the Appeal Board. The Panel noted that there had been a number of cases involving Schering-Plough recently. The Panel considered that taking all the circumstances into account this case was not one that warranted a formal report to the Code of Practice Appeal Board.

APPEAL BY SCHERING-PLOUGH

Schering-Plough noted the Panel's view that the claim '… for the past 50 years Schering-Plough has striven to bring improved anti-allergic medicines to the NHS. Our latest development in this field is NeoClarityn, desloratadine, a purified development of Clarityn' implied that NeoClarityn was an improved version of Clarityn and was therefore in breach of the Code.

Schering-Plough submitted that no such implication was made. If one considered each of the statements in the letter, they did not, individually or collectively, make a claim for the superiority or otherwise of NeoClarityn over Clarityn.

That Schering-Plough had striven to bring improved medicines to the NHS, like every other company, was accurate, and was a reflection of the company's ambition. It was not a statement that it was necessarily successful in this endeavour. This aspirational statement was simply a positive way of introducing the company.

This introduction appeared to have been linked to the next sentence to shape the Panel's ruling. The next sentence stated 'Our latest treatment is NeoClarityn, desloratadine, a purified development of Clarityn'. Again, Schering-Plough strongly disputed that there was anything in this sentence that implied a claim of superiority of NeoClarityn over Clarityn. NeoClarityn was the latest anti-allergic medicine Schering-Plough had. It awaited further evidence to determine whether it was clinically superior to Clarityn. Until this evidence arrived, Schering-Plough would not make comparative clinical claims between the two medicines.

There appeared to be a concern that the word 'development' in the phrase 'a purified development of Clarityn', implied a clinical superiority. Examination of the phrase in more detail was crucial to the realisation that Schering-Plough did not intend to imply any clinical superiority of NeoClarityn over Clarityn.

Firstly, it was scientifically accurate to state that NeoClarityn was a purified development of Clarityn. NeoClarityn contained desloratadine, the active metabolite of loratadine, without the host of weaker metabolites and intermediaries that Clarityn produced *in vivo*.

Secondly, in reading both the initial complaint and the Panel's ruling there appeared to be an assumption that all developments were necessarily better. Personal as well as professional experience made most of us realise this was not necessarily so.

To reinforce this point, Schering-Plough noted that its original response gave various dictionary definitions of development, such as 'a fact, event, or happening' to demonstrate the neutrality of the word. The Panel consulted another dictionary and came back with the definitions of 'evolution, growth, a developed form of product, a stage of advancement'. These definitions again all denoted a change but, similar to the Schering-Plough definitions, did not necessarily denote a positive change.

'Evolution' was a responsive adaptation to the environment, no judgement was made as to whether it was a positive or negative change, as the evolutionary history of the dodo would attest. 'Growth' might be a good thing or bad thing as the different views of a member of Weight Watchers to a

proud parent of a baby watching the scales would attest. 'A developed form of product' seemed a rather circular definition but again there was no value judgement attached to it as to whether it was a better form or not, more poorly developed or not. 'A stage of advancement' could clearly denote a positive or negative stage as in a career advancement or the stages of advancing of cancer.

Schering-Plough submitted clearly the term 'development' was a neutral noun, and required a qualifying adjective to denote whether it was better, worse or the same.

Schering-Plough accepted that in the past it had erred in its promotional efforts with NeoClarityn. When it had erred it had readily accepted its mistakes and striven to improve. The company found it difficult to accept an error here. The text taken as a whole, or in individual phrases, did not lead to the conclusion that it was suggesting that NeoClarityn was clinically superior to Clarityn.

The second claim the Panel found at fault was 'This new treatment for your patients with seasonal allergic rhinitis and chronic idiopathic urticaria is exactly the same price as Clarityn and will therefore not have an impact on your prescribing budget'. Schering-Plough submitted that the second claim at issue was surely clear to prescribers. The piece specifically referred to seasonal allergic rhinitis and chronic idiopathic urticaria. It was true that as the tablets were the same price, switching from one to the other for these patients was cost-neutral.

The letter clearly referred to the prescribing budget for seasonal allergic rhinitis and chronic idiopathic urticaria. It required a significant shift of thought to bring in the budget for perennial allergic rhinitis and claim that this would change as a result of a shift to a new treatment for seasonal allergic rhinitis and chronic idiopathic urticaria.

Schering-Plough had had hundreds of queries on its NeoClarityn help line and its medical information inquiry service since it announced the discontinuation of Clarityn. It was unable to find a single case of a health professional misunderstanding this statement.

Schering-Plough therefore disagreed with the Panel's ruling that this claim was in breach of Clause 7.

Schering-Plough recognised that the rulings were based on an interpretation of the implications of words, and it recognised that words might give a different impression in context from out of context.

Schering-Plough's intention was to inform health professionals of the discontinuation of Clarityn and inform them of an alternative for their patients with seasonal allergic rhinitis and chronic idiopathic urticaria. The company was careful not to imply that the switch was due in any way to superiority of NeoClarityn over Clarityn – but simply and honestly made it clear this was a commercial decision on Schering-Plough's part. Such an explanation would not be needed were Schering-Plough implying that prescribers should change their prescribing habits because of NeoClarityn's clinical superiority.

Schering-Plough recognised it had made errors in the past with NeoClarityn promotional material but did not feel that this was such a case.

COMMENTS FROM SCHWARZ PHARMA

Statement '… for the past 50 years Schering-Plough has striven to bring improved anti-allergic medicine to the NHS. Our latest development in this field is NeoClarityn, desloratadine, a purified development of Clarityn'

Schwarz noted that Schering-Plough claimed that these two sentences did not imply that NeoClarityn was an improved version of Clarityn but pointed out the following:

1 This was a piece of promotional material. The 'intent' of promotional material, by definition, was to promote a product, in this case NeoClarityn. All statements in it would therefore be read in this context, not just by Schwarz, but also by health professionals. As Schering-Plough stated in its appeal, '… we recognise that words may give a different impression in context from out of context'. In the context of a promotional mailing, these two sentences in sequence gave the impression that NeoClarityn was an 'improved anti-allergic medicine'.

2 That the word 'development' could mean good or bad change was not relevant to this complaint. As stated previously by Schering-Plough, context was all-important. Was it seriously suggesting that a pharmaceutical company would mention a 'latest development' in a piece of promotional material if it were not a positive one? Whilst 'evolution' and 'advancement' might be negatives in other contexts, both were singularly positive adjectives when describing drug development. To Schwarz's knowledge no one had ever described a medicine as an advance if it was a more toxic or less efficacious agent than its predecessor.

3 In terms of context, Schwarz noted that the NeoClarityn promotional campaign was launched in the UK with the slogans 'Clarityn with extra clout' and '40 times more potent than Clarityn'. The health professionals had already been exposed to these claims before receiving this mailing. The interpretation of any areas of ambiguity in the mailing would have been influenced by these prior (unsubstantiable) claims.

4 Both Schwarz and the Panel read it to imply that NeoClarityn was an improved anti-allergic medicine, which indicated that it could be reasonably interpreted this way. The Code specifically stated that claims must be unambiguous and reflect the evidence clearly. Therefore, even if it was accepted that it had been 'misinterpreted' by these two disparate groups of people, it was still in breach of Clause 7.2 because it could be interpreted this way, even if this was not Schering-Plough's intent.

Statement 'This new treatment for your patients with seasonal allergic rhinitis and chronic idiopathic urticaria is exactly the same price as Clarityn, and will therefore not have an impact on your prescribing budget'

1 Schwarz noted that Schering-Plough argued that

the piece 'clearly refers to the prescribing budget for seasonal allergic rhinitis and chronic idiopathic urticaria'. Why should the reader assume this? It was not stated clearly, and not all patients with these conditions were treated with Clarityn. It was more reasonable to infer that the piece referred to the Clarityn prescribing budget, as that was what the mailing was communicating – the discontinuation of Clarityn and its replacement with NeoClarityn.

2 Not stating something could be just as misleading as stating something untrue. By not mentioning the difference in indication Schering-Plough had implied that the prescribing budget for Clarityn would be unchanged, not just the budget for Clarityn used in seasonal allergic rhinitis and chronic idiopathic urticaria. Had Schering-Plough truly been attempting to 'inform' health care professionals, it would have made it clear that some other alternative would have to be found for perennial allergic rhinitis.

Schering-Plough had appealed on the basis that it was not its intent to breach the Code in this way and that the text could be interpreted differently. However, if Schwarz had interpreted it this way and the Panel had interpreted it in exactly the same way, then it was not unreasonable to assume that other readers had also done so. It was precisely why words like 'clearly' and 'unambiguous' were included in Clause 7.

Schwarz did not accept the somewhat disingenuous argument that development was a 'neutral' word in this context, nor that the first sentence in question was 'simply a positive way of introducing ourselves'. However, even if that was genuinely the intent, it didn't alter the fact that the text could be legitimately interpreted the way that Schwarz and the Panel had.

APPEAL BOARD RULING

The Appeal Board noted the layout and content of the first claim at issue which read:

'… for the last 50 years Schering-Plough has striven to bring improved anti allergic medicine to the NHS.

Our latest treatment in this field is NeoClarityn, desloratadine, a purified development of Clarityn …'.

Each party had misquoted the claim replacing 'treatment' with 'development'. The error had been repeated by the Panel as part of its ruling. Other parts quoted the claim as it appeared in the letter.

The Appeal Board considered that the claim at issue and the letter as a whole gave the impression that NeoClarityn was an improved medicine compared to Clarityn and there was no evidence that this was so. There were no *in vivo* clinical trials comparing Clarityn and NeoClarityn and the EPAR concluded that there was no difference in efficacy between the two products. The Appeal Board considered that the claim was misleading and not capable of substantiation as alleged. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

With regard to the second claim at issue 'This new treatment for your patients with seasonal allergic rhinitis and chronic idiopathic urticaria is exactly the same price as Clarityn and will therefore not have an impact on your prescribing budget', the Appeal Board noted the differences between the products' licensed indications; that for NeoClarityn was more restrictive as unlike Clarityn it was not licensed for perennial allergic rhinitis. The Appeal Board considered that it had not been made sufficiently clear that not all patients on Clarityn could be transferred to NeoClarityn. The claim implied that the change would have no impact on the prescribing budget which was not so. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.3. The appeal on this point was unsuccessful.

The Appeal Board noted the previous cases concerning the promotion of NeoClarityn by Schering-Plough. In Case AUTH/1210/7/01, which concerned a breach of undertaking, Schering-Plough had been required to undergo an audit of its procedures in relation to the Code. That audit had taken place on 23 October 2001. The report had been considered by the Appeal Board at its meeting in November. The Appeal Board had noted the action taken by Schering-Plough and that it had not implemented some of the recommendations from the previous audit in October 1998. The Appeal Board did not consider that the circumstances warranted reporting Schering-Plough to the ABPI Board of Management. The Appeal Board had decided that Schering-Plough should undergo another audit in six months (May 2002) to check that the recommendations of the recent audit had been implemented. On this basis the Appeal Board had decided that no further action was necessary. A subsequent audit had been arranged for 9 May.

The Appeal Board noted that the letter at issue in the present case had been distributed in September 2001 prior to the latest audit. Schering-Plough had subsequently appealed the Panel's rulings in the present case. The Appeal Board was very concerned about Schering-Plough's promotion of NeoClarityn. There had been a number of cases and the company had repeatedly been ruled in breach of the Code for similar issues, albeit not exactly the same. One case had however involved a breach of undertaking. The Appeal Board considered that the circumstances warranted reporting the company to the ABPI Board of Management pursuant to Paragraph 12.1 of the Constitution and Procedure for it to decide whether further sanctions should be applied.

REPORT TO THE ABPI BOARD OF MANAGEMENT

The ABPI Board of Management was very concerned about the conduct of Schering-Plough. The number of cases involving NeoClarityn and the similarity between the complaints were noted. The ABPI Board noted that Schering-Plough had been audited twice by the Authority and a further audit was to take place in May 2002. The ABPI Board requested sight of the May 2002 audit report. The ABPI Board noted that the Constitution and Procedure was such that the Appeal Board could report companies to the ABPI Board regardless of whether or not there was an appeal.

As this was a serious matter the ABPI Board decided that Schering-Plough should be reprimanded and details of that reprimand published.

On receipt of the audit report, the ABPI Board decided that no further action was necessary.

Complaint received **10 October 2001**

PMCPA proceedings completed **11 February 2002**

ABPI Board proceedings completed **28 May 2002**

CASE AUTH/1241/10/01

CHIRON CORPORATION v FOREST LABORATORIES

Promotion of Colomycin

Chiron Corporation complained about the promotion of Colomycin (colistin) by Forest Laboratories, the items at issue being a booklet and a leavepiece. The booklet, entitled 'Cystic Fibrosis Care: Developing the Information Base for the 'New NHS", contained a report by Professor Nick Bosanquet. The last page of the report featured a chart which gave the average cost of treating cystic fibrosis (CF) according to severity and how that cost would increase if Colomycin was replaced by Tobi (Chiron's tobramycin). The leavepiece featured a similar chart.

Chiron stated that the Colomycin summary of product characteristics (SPC) clearly stated that the dose for aerosolisation in adults was 2 mega units (2MU) tds. Therefore Forest could not promote an annual dosing schedule of 1MU bd (even though it might be used in clinical practice) unless it amended the terms of the licence. It should be stated clearly on the material that the daily dose of 2MU tds was the only licensed regimen for adults with CF and hence the costings should include a range based on this licensed daily dose.

The Panel noted that Colomycin injection should only be used to treat severe systemic or localised infections caused by sensitive Gram-negative organisms eg respiratory infection and septicaemia. The injection could be given by aerosol inhalation, as adjunct therapy in patients already receiving standard antibiotic therapy. When administered by aerosol the adult daily dosage was as per the normal recommendations for systemic treatment ie 2MU every eight hours. The Panel did not accept Forest's submission that the use of Colomycin in the treatment of CF represented a highly abnormal situation such that the normal dosage requirements did not apply. Both the booklet and the leavepiece contained cost comparison charts which referred to the use of Colomycin 2MU daily. The Panel considered that this dose was inconsistent with the dosage in the SPC. It was immaterial that the prescribing information for Colomycin, which referred to the use of 2MU every eight hours, was included in the leavepiece. A breach of the Code was ruled.

Chiron noted that assumptions made in an economic evaluation must be consistent with the marketing authorization. Forest had presented the relative costs of Colomycin and Tobi such that treatment with Colomycin appeared less expensive than would actually be the case. This was unfair. The costings for Tobi were based on the licensed recommendations for chronic maintenance therapy in CF. Forest had referred to a year's treatment with Tobi, involving six cycles of a month on followed by a month off treatment. The comparative costings for Colomycin should have been based on one year's chronic maintenance therapy using continuous daily dosing since Forest did not have a licence for intermittent therapy.

The Panel noted from its SPC that Tobi was indicated for the long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in CF. A cycle of 28 days of active therapy followed by 28 days of rest from treatment should be maintained. Safety and efficacy had been assessed for up to 96 weeks (12 cycles). The Colomycin SPC stated that 2MU should be administered, by injection or aerosol, every eight hours but gave no indication as to the duration of such therapy. The only reference to a duration of therapy was with regard to the product being administered as a bladder irrigation when it was recommended that a minimum of five days' treatment be given.

The cost comparison charts in the booklet and in the leavepiece referred to the use of Colomycin in CF, 2MU daily for three months at a time, twice a year. The Panel had considered above that reference to a dose of 2MU daily was inconsistent with the dosage particulars listed in the Colomycin SPC, in breach of the Code.

As to whether Colomycin had a licence for intermittent therapy, the SPC was silent; it recommended neither intermittent therapy nor continuous therapy. The Panel considered that in the circumstances reference to intermittent therapy was not inconsistent with the particulars listed in the Colomycin SPC and so the cost comparison was not misleading in this regard as alleged. No breach of the Code was ruled.

Upon appeal by Chiron, the Appeal Board noted Forest's submission at the appeal hearing that Colomycin had been in use for many years. The way in which it was used was driven by clinicians' personal experience as opposed to being dictated by the results of randomized clinical trials. In the management of CF patients usage ranged from 2MU daily on an intermittent basis up to 2MU three times

daily continuously. The Appeal Board accepted that the cost comparison represented one end of the spectrum of Colomycin usage in CF. With regard to cost it represented the lower end of the scale. Intermittent use of 2MU daily had been compared with the only licensed dose of Tobi. The Appeal Board did not consider that the cost comparison compared like with like and in that regard it was unfair. A breach of the Code was ruled.

Chiron alleged a breach of the Code because Forest had failed to ensure that its representative at a meeting was aware that the company had withdrawn the promotional material from use. The representative was inadequately briefed that these materials did not comply with the Code. The Panel noted that the parties' accounts differed. Chiron had stated that the booklet and the leavepiece had been used at the meeting; Forest was adamant that they had not. It appeared that there had been an agreement between the two companies in August that the material would no longer be distributed. On the information provided, however, it was impossible to determine whether the material had subsequently been used in October. In the circumstances the Panel ruled no breach of the Code.

Upon appeal by Chiron, the Appeal Board noted that the Code required companies to prepare detailed briefing material for medical representatives on the technical aspects of each medicine which they would promote. The material referred to 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 Appeal Board considered that instructions issued to representatives about pieces of promotional material to be withdrawn would be included in this description of briefing material. The Appeal Board noted that this case related to Forest voluntarily agreeing with Chiron that it would stop using the material at issue. At the time of the meeting the material had not been ruled in breach of the Code. Forest had not been required to withdraw it and there was no breach of undertaking.

The Appeal Board noted that although there remained a conflict of evidence with regard to the availability of material at the meeting in question, the medical representative was clear that she knew that she had to stop using certain promotional items. In the Appeal Board's view the representative had been adequately briefed. The Appeal Board upheld the Panel's ruling of no breach of the Code.

Chiron Corporation Limited complained about the promotion of Colomycin (colistin) by Forest Laboratories Europe. There were two items at issue; the first was an A4 booklet (ref G1215/WBR/Aug2000) entitled 'Cystic Fibrosis Care: Developing the Information Base for the 'New NHS'' which contained a report by Professor Nick Bosanquet. The last page of the report featured a chart which gave the average cost of treating cystic fibrosis (CF) according to severity and how that cost would increase if Colomycin was replaced by Tobi (Chiron's branded tobramycin). The second item was an A5 folded leavepiece (ref G1224/WBR/Sept2000) which featured a similar chart to that contained within the report.

Chiron stated that it had had protracted correspondence with Forest concerning the cost chart. The basis of its complaint was that the cost of Colomycin was based on a treatment regimen other than that licensed for the product. In mid August Chiron received an undertaking from Forest that the material was no longer being distributed and that it would be modified when reprinted 'to indicate a wider variety of regimens'.

However Chiron alleged that at the Scottish CF meeting in Stirling Hospital on 12 October 2001, the materials were still being made available from the Forest stand. Chiron considered that future attempts at reconciliation with Forest concerning these materials would be unproductive.

Chiron stated that Forest had previously argued that the booklet was an independent publication, but the act of providing it from a company stand, printing it with a company reference number and referring to it in the leavepiece meant that it was subject to the Code.

Forest stated that neither the booklet nor the leavepiece was distributed at the Scottish CF meeting. The company confirmed that it had discussed the leavepiece with Chiron. No admission was made that any of the information was inaccurate but in order to avoid potential conflict it was agreed that the document, when reprinted, would be re-worded in order to avoid the possible confusion. At that time it was also confirmed that the sales representatives would no longer be distributing the document, and the matter was closed. Under the circumstances Forest did not consider that there was a case to answer.

In a letter to Forest requesting that it responded to the substantiative issues of the complaint the Authority pointed out that informal agreements between companies did not preclude a subsequent complaint.

1 Promotion outside the licence

COMPLAINT

Chiron noted that Clause 3.2 of the Code required that, *inter alia*, the promotion of a medicine must not be inconsistent with the particulars listed in its summary of product characteristics (SPC).

The Colomycin SPC clearly stated that the dose for aerosolisation in adults was 2 mega units (2MU) tds. Therefore Forest could not promote an annual dosing schedule of 1MU bd (even though it might be used in clinical practice) unless it amended the terms of the licence. It should be stated clearly on the material that the daily dose of 2MU tds was the only licensed regimen for adults with CF and hence the costings should include a range based on this licensed daily dose.

RESPONSE

Forest submitted that the leavepiece clearly and prominently stated on the front cover that it was

adapted from the findings of Professor Bosanquet. It was also clearly stated that the comparison was of an estimated annual treatment (including all medicines – oral, inhaled and IV antibiotics) using Colomycin or tobramycin (preservative free tobramycin solution for nebulisation) and that Colomycin dosage used in this assessment at that centre was 2MU daily.

Forest noted that the Colomycin SPC explicitly stated that indicated doses were for normal use of the antibiotic. The management of infection in CF was a highly abnormal situation and quite unlike any other therapeutic modality. Clinicians treating pseudomonal lung infections in CF had had years of experience in using Colomycin and they, together with the microbiologists dictated the most appropriate dosage and route of administration to suit the individual situation. Whilst the company accepted that the Colomycin SPC provided a normal dosage recommendation of 2MU three times daily this was not necessarily the conventional dosage for all patients in all conditions. Forest submitted that it was reasonable for the clinician concerned to interpret the SPC accordingly. As would be seen from the leavepiece the company did not make any recommendations or promotional claims for efficacy and/or safety. However, the relevant prescribing information was printed on the leavepiece so that there could be no confusion amongst the intended audience of highly skilled clinicians involved in the treatment of CF.

PANEL RULING

The Panel noted that the booklet had been used by Forest. It appeared that it had been printed by the company and had been distributed by the company. In the Panel's view it was being used to promote Colomycin and was therefore subject to the Code.

The Panel noted that Colomycin injection should only be used to treat severe systemic or localised infections caused by sensitive Gram-negative organisms eg respiratory infection and septicaemia. The injection could be given by aerosol inhalation, as adjunct therapy in patients already receiving standard antibiotic therapy. When administered by aerosol the adult daily dosage was as per the normal recommendations for systemic treatment ie 2MU every eight hours (ref Colomycin Injection SPC, Electronic Medicines Compendium, last updated 3 December 2001). The Panel did not accept Forest's submission that the use of Colomycin in the treatment of CF represented a highly abnormal situation such that the normal dosage requirements, as stated in the SPC, did not apply.

Both the booklet and the leavepiece contained cost comparison charts which referred to the use of Colomycin 2MU daily. The Panel considered that this dose was inconsistent with the dosage particulars listed in the Colomycin SPC. It was immaterial that the prescribing information for Colomycin for aerosol therapy and for Colomycin for injection, which referred to the use of 2MU every eight hours, was included in the leavepiece. A breach of Clause 3.2 was ruled.

During its consideration of this case the Panel was concerned that the booklet, which had been produced by Forest and which referred to Colomycin, did not include the prescribing information for the product as required by Clause 4.1. In addition there was no statement on the booklet to indicate that it had been sponsored by a pharmaceutical company as required by Clause 9.9 of the Code. The booklet had the appearance of an official publication and so might be considered to be disguised promotion in breach of Clause 10.1 of the Code. The Panel requested that Forest be advised of its concerns.

2 Unfair cost comparison

COMPLAINT

Chiron noted that the Code stated that assumptions made in an economic evaluation must be consistent with the marketing authorization. The way in which Forest had presented the relative costs of Colomycin and Tobi made it appear that treatment with Colomycin was less expensive than would actually be the case. This was therefore not a fair cost comparison under the Code. The costings for Tobi were based on the licensed recommendations for chronic maintenance therapy in CF. Forest had referred to a year's treatment with Tobi, involving six cycles of a month on followed by a month off treatment (Tobi SPC). The comparative costings for Colomycin should also have been based on chronic maintenance therapy over the same period of one year and this should have involved continuous daily dosing, since Forest did not have a licence for intermittent therapy (Colomycin SPC). Chiron alleged a breach of Clause 7.2 of the Code.

RESPONSE

Forest noted that the Colomycin SPC explicitly stated that indicated doses were for normal use of the antibiotic. The management of infection in CF was a highly abnormal situation and quite unlike any other therapeutic modality. Clinicians treating pseudomonal lung infections in CF had had years of experience in using Colomycin and they, together with the microbiologists dictated the most appropriate dosage and route of administration to suit the individual situation. Whilst the company accepted that the Colomycin SPC provided a normal dosage recommendation of 2MU three times daily this was not necessarily the conventional dosage for all patients in all conditions. Forest submitted that it was reasonable for the clinician concerned to interpret the SPC accordingly. As would be seen from the leavepiece the company did not make any recommendations or promotional claims for efficacy and/or safety. However, the relevant prescribing information was printed on the leavepiece so that there could be no confusion amongst the intended audience of highly skilled clinicians involved in the treatment of CF.

Forest stated that it was a logical conclusion that there was no breach of Clause 7.2. The information was accurate in that it was a factual report of what occurred in Professor Bosanquet's study and was consequently well balanced. The information was also fair since there was no conceivable scenario in

which treating a patient with Colomycin therapy would not be considerably cheaper than the use of Tobi in similar circumstances.

PANEL RULING

The Panel noted that Tobi was indicated for the long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in CF. A cycle of 28 days of active therapy followed by 28 days of rest from treatment should be maintained. Safety and efficacy had been assessed in controlled and open label studies for up to 96 weeks (12 cycles) (ref Tobi SPC). The Colomycin SPC stated that 2MU should be administered, by injection or aerosol, every eight hours but gave no indication as to the duration of such therapy. The only reference to a duration of therapy in the Colomycin SPC was with regard to the product being administered as a bladder irrigation when it was recommended that a minimum of five days' treatment be given.

The cost comparison charts in the booklet and in the leavepiece referred to the use of Colomycin in CF, 2MU daily for three months at a time twice a year. The Panel had considered in point 1 that reference to a dose of 2MU daily was inconsistent with the dosage particulars listed in the Colomycin SPC, in breach of the Code.

As to whether Colomycin had a licence for intermittent therapy, the SPC was silent on the matter. It recommended neither intermittent therapy nor continuous therapy. The Panel considered that in the circumstances reference to intermittent therapy was not inconsistent with the particulars listed in the Colomycin SPC and so the cost comparison was not misleading in this regard as alleged. No breach of Clause 7.2 of the Code was ruled.

The Panel noted that the complaint related to whether Colomycin was licensed for intermittent therapy. It had not, therefore, been required to examine whether such therapy represented accepted clinical practice throughout the UK. Forest had thus not been required to substantiate its recommendation to use Colomycin for 3 months at a time twice a year. The Panel noted that the material had been withdrawn. Nevertheless, the Panel requested that Forest should be advised to ensure that it had such substantiation if it made such a claim in the future.

APPEAL BY CHIRON

Chiron noted that the supplementary information to Clause 7.2 stated that 'valid comparisons can only be made where like is compared with like'. The company expanded on its assertion that it was misleading to compare two, 3 month courses of colistin in a year with a year's month on month off treatment with Tobi.

Tobi was licensed for the management of chronic pulmonary infection due to *P. aeruginosa*. Patients with chronic *P. aeruginosa* infection required chronic active treatment with nebulised antibiotics. Chiron had demonstrated that month on month off treatment was appropriate to treat chronic infection in large randomised controlled studies (Ramsey *et al*, 1999). The regimen was approved by the Medicines Control Agency (MCA) and appeared in the Tobi SPC.

The dosing regimen of intermittent, three month treatment courses with colistin was recommended only for first and intermittent colonisation with *P. aeruginosa* according to the Cystic Fibrosis Trust Guidelines, 2000. These guidelines on antibiotic use clearly stated on page 18 that as soon as infection with *P. aeruginosa* became persistent, colistin should be given continuously. Thus Chiron reasserted that the cost comparison was not comparing like with like. Forest was comparing a dose regimen used in intermittent colonisation (Fredriksen *et al* 1997, Cystic Fibrosis Trust guidelines, 2000) with a dose regimen for Tobi licensed only for chronic maintenance therapy. There were no data to support the use of intermittent courses of colistin in chronic *P. aeruginosa* infection in CF and this was not the current UK standard of care.

Chiron noted that the Panel had already ruled in point 1 that the promotion of 2MU daily colistin was not in line with the SPC and was in breach of Code. In Forest's cost comparison this unlicensed dose for colistin was being compared with one for Tobi that was licensed. In this respect too the cost comparison was unfair because it was not comparing 'like with like' and was in breach of Clause 7.2 of the Code.

COMMENTS FROM FOREST

Forest stood by its original response, that the data in the leavepiece was based on independent findings by Professor Bosanquet which were results of a pharmacoeconomic study based on actual usage data. The centre in question was chosen as it was a large CF centre and as such represented, at the time of the evaluation, current practice. The price comparisons, therefore, were an accurate representation of the cost of treating CF patients with Colomycin over a twelve month period. The cost for treating a patient with Tobi was in line with the dosage requirements data on its SPC.

Forest noted that in its ruling the Panel considered that the reference to a dose of 2MU daily was inconsistent with the dosage particulars listed in the Colomycin SPC. However, with regard to whether Colomycin had a licence for intermittent therapy, the SPC was silent on this matter and it recommended neither intermittent nor continuous therapy. As a result the Panel considered that reference to intermittent therapy was not inconsistent with the particulars listed in the Colomycin SPC. Forest noted that it had given a signed undertaking to accept the Panel's ruling and had submitted a variation to the MCA to modify its SPC in line with current clinical practice.

It seemed clear to Forest, therefore, that the Panel had made a ruling based entirely on what was contained within the current Colomycin SPC. In the circumstances, by introducing a set of guidelines published by the Cystic Fibrosis Trust, Chiron was attempting to suggest that a charitable organisation which had no regulatory or other official standing, could over-rule both the Panel's ruling and also an SPC forming part of the marketing authorization agreed by the MCA. Current guidelines from the

Cystic Fibrosis Trust and European Cystic Fibrosis Working Group were also silent about the exact duration of therapy. Forest stated that it was bound by its SPC not independent guidelines.

FURTHER COMMENTS FROM CHIRON

Chiron stated that the argument that Professor Bosanquet's findings were independent was irrelevant; it was the promotional use of them that was in question.

Chiron noted that it was general clinical practice to use colistin continuously for CF patients chronically colonised with *P. aeruginosa* (for shorter or longer periods) rather than month on, month off. SPCs of products intended to be used continuously did not normally state this. This was assumed unless there were instructions to the contrary, as with Tobi.

Whatever time period was chosen for a cost comparison between the two products, it should be the same for both. During this time, Tobi would be dosed on half the number of days on which Colomycin was dosed. Forest had chosen to give the cost of care for a twelve month period of use of Tobi so it should compare it with twelve months of (daily) Colomycin. Forest could only legitimately do so at a dose of 6MU per day as this was all it had licensed.

Chiron stated that the relevance of the guidelines produced by the Cystic Fibrosis Trust, which despite Forest's contention was an influential body, was that they informed clinical practice. The Cystic Fibrosis Trust Guidelines supported Chiron's contention that Forest's product, Colomycin, was generally used continuously by inhalation.

APPEAL BOARD RULING

The Appeal Board noted Forest's submission at the appeal hearing that Colomycin had been in use for many years. The way in which it was used was driven by clinicians' personal experience as opposed to being dictated by the results of randomized clinical trials. In the management of CF patients there was a spectrum of usage which ranged from 2MU daily on an intermittent basis up to 2MU three times daily continuously. Conversely Tobi had been introduced only relatively recently; its specific indication was in the long-term management of chronic pulmonary infection due to *P. aeruginosa* in CF patients aged 6 years and older. The licensed dose for Tobi was 300mg twice daily for 28 days followed by 28 days of no Tobi treatment.

The Appeal Board accepted that the cost comparison, based on Professor Bosanquet's study, represented one end of the spectrum of Colomycin usage in CF. With regard to cost it represented the lower end of the scale. Intermittent use of 2MU daily had been compared with the only licensed dose of Tobi. The Appeal Board did not consider that the cost comparison compared like with like and in that regard it was unfair. A breach of Clause 7.2 was ruled. The appeal on this point was successful.

During its consideration of this case the Appeal Board noted that the four cost comparison graphs which appeared on the leavepiece used different vertical scales. The Appeal Board was concerned that comparison of one graph with the others was misleading due to the different scales used. The Appeal Board requested that its concerns be drawn to Forest's attention.

3 Briefing material

COMPLAINT

Chiron alleged a breach of Clause 15.9 on the grounds that Forest had failed to ensure that its representative at the Stirling CF meeting was aware that the company had withdrawn the promotional material from use. The representative was inadequately briefed that these materials did not comply with the Code.

RESPONSE

Forest stated that it emphatically maintained that the materials were not used at the meeting.

PANEL RULING

The Panel noted that the parties' accounts differed. Chiron had stated that the booklet and the leavepiece had been used at the Stirling cystic fibrosis meeting; Forest was adamant that they had not. It appeared that there had been an agreement between the two companies in August that the material would no longer be distributed. On the information provided, however, it was impossible to determine whether the material had subsequently been used in October. In the circumstances the Panel ruled no breach of Clause 15.9 of the Code.

APPEAL BY CHIRON

Chiron stated that as a highly ethical pharmaceutical company it strongly refuted the allegation that it 'falsified' information relating to the Stirling CF meeting. Although the company did not have a stand at the meeting it provided sponsorship. Its UK medical director and its product manager attended the meeting although they were not required to register. Chiron provided a written statement supporting the fact that both of its employees picked up the materials in question from the Forest stand at the Stirling meeting on 12 October 2001.

Chiron could only assume that the Forest representative was trying to avoid disciplinary action or there was collusion within the company to misrepresent itself to the Authority. Chiron believed that this type of conduct brought the industry into disrepute.

As previously stated Chiron believed it had reached a written agreement with Forest to withdraw and reprint its respective materials although as stated it reserved the right to complain to the Authority if the materials were used again, which they were.

COMMENTS FROM FOREST

Forest referred to the Panel's ruling and noted that a

judgement was made that on the information provided it was impossible to determine whether the material had subsequently been used in October. Chiron had now provided travel documentation and a signed statement by the two people who had alleged the offence, that they attended the meeting and allegedly were able to pick up material from the stand. In contrast Forest's representative, who had been with the company for over four years and was of upstanding character, had stated that any copies of the material concerned were still at a hotel elsewhere and therefore it was physically impossible for material of this nature to have been at the meeting in Stirling on 12 October.

Forest noted that it had informed Chiron in September 2001 that it had ceased distributing the item, but clearly, it was in use prior to that date. A letter from the hotel showed that it was used at the meeting on 6 September 2001, prior to Forest's undertaking to Chiron to cease using the material. As a result Forest had no doubt that copies of both of the pieces of literature at issue might well be in Chiron's possession.

Forest noted that at no time had it ever stated that Chiron 'falsified' information relating to the Stirling CF meeting. The company noted, however, that in the undated statement made by Chiron's medical director and product manager they referred to 'the stand staffed by Forest sales representatives'. Again in this aspect they were also mistaken since the representative was the only person from Forest at the meeting.

The fundamental issue was that there was no evidence whatsoever to support Chiron's claim, and the allegation could not be substantiated. It was supported only by Chiron's word and could not be verified in any way.

Conversely Forest noted that it had provided a statement and a paper-trail confirming that the promotional item was not displayed. Any consideration of the assertion of a company medical director versus a company sales representative should not be relevant as it brought into question the credibility of both parties.

FURTHER COMMENTS FROM CHIRON

Chiron stated that the letter from the hotel was no proof of what was left behind. It did not prove that others were not on the stand at the Stirling meeting. If Forest believed its representative, it must believe that Chiron's medical director and product manager falsified information provided to the Authority when they stated that they picked up the item in Stirling. Chiron stated that it did not actually know whether there was one or more representatives present at this meeting, however the appeal was related to the presence of material at the meeting that should have been withdrawn, not the number of representatives in attendance.

APPEAL BOARD RULING

Clause 15.9 of the Code required companies to prepare detailed briefing material for medical representatives on the technical aspects of each medicine which they would promote. The relevant supplementary information stated that the material referred to in this clause 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 Appeal Board considered that instructions issued to representatives about pieces of promotional material to be withdrawn would be included in this description of briefing material. The Appeal Board noted that this case related to Forest voluntarily agreeing with Chiron that it would stop using the material at issue. At the time of the meeting the material had not been ruled in breach of the Code. Forest had not been required to withdraw it and there was no breach of undertaking.

In a prepared statement, read out at the appeal hearing, Forest's medical representative was quite clear that she had been told by the Colomycin product manager to stop using promotional items which referred to cost comparisons between Colomycin and Tobi. On questioning by the Appeal Board the representative stated that she had received these instructions by telephone and also by letter. Forest's other representatives at the appeal hearing referred to instructions being sent by e-mail. Forest did not provide copies of either the letter or the e-mail.

The Appeal Board noted that although there remained a conflict of evidence with regard to the availability of material at the meeting in question, the medical representative was clear that she knew that she had to stop using certain promotional items. In the Appeal Board's view the representative had been adequately briefed and thus there could be not be a breach of Clause 15.9 as alleged. The Appeal Board upheld the Panel's ruling of no breach of Clause 15.9. The appeal on this point was unsuccessful.

During its consideration of this case the Appeal Board noted that the representative had been told in early September 2001 to stop using promotional items which referred to cost comparisons between Colomycin and Tobi. The material at issue had last been used by the representative at a meeting a few days prior to her receiving this instruction; it had been inadvertently left in a box at the hotel. The Appeal Board was very concerned to note that that material was still waiting to be collected from the hotel at the end of February 2002. Companies should have procedures in place to ensure that promotional material was quickly and entirely withdrawn from use even when such withdrawal was as a consequence of a voluntary agreement. The Appeal Board requested that Forest be advised of its concerns in this regard.

Complaint received **24 October 2001**

Case completed **4 April 2002**

CASE AUTH/1259/11/01

PHARMACIA v ALLERGAN

Promotion of Lumigan

Pharmacia alleged that a presentation entitled 'Mechanisms of Action of Prostaglandins and Prostanoids', given by an employee of Allergan at an independent ophthalmology symposium in September 2001, breached various aspects of the Code. Pharmacia stated that Allergan's product Lumigan (bimatoprost) was the subject of the presentation and that Allergan had declined its request for a copy of the slides, providing only a list of citations.

The Panel noted that Pharmacia had not requested substantiation for any of the information, claims or comparisons contained within slides used in the presentation. Pharmacia had in fact requested copies of the slides themselves and in doing so had referred to the requirement in the Code for substantiation to be provided on request and had stated that as promotional claims were made, the presentation was subject to the Code. Allergan did not agree that the matter came within the scope of the Code but nevertheless provided a list of citations supporting the presentation. The Panel did not consider that Allergan's failure to give Pharmacia copies of the actual slides meant that Allergan had failed to substantiate the information, claims or comparisons featured in them. No breach of the Code was ruled in this regard.

Pharmacia alleged that one slide implied that the concept of 'prostamides' as a distinct group from prostaglandins was an accepted nomenclature, similar to the alpha and beta classification of adrenergic receptors. This was not an established classification, supported by published independent peer-reviewed studies. Pharmacia alleged that this represented a breach of the Code with respect to emerging scientific opinion.

The Panel considered that the impression from the slide in question was that the lipid family receptors, cannabinoid, prostaglandin and prostamide, were as well established as the β_1, β_2, a_1 and a_2 subdivisions of the adrenergic family receptors. Allergan's response referred to prostamides as a new class of medicines. The Panel noted that the audience was made up of experts in the field of glaucoma. Such an audience would be familiar with the concepts presented. The Panel decided that in the circumstances the slide was not unreasonable. The issue had been treated in a balanced manner. No breach of the Code was ruled. This ruling was appealed by Pharmacia.

The Appeal Board considered that only scientific evidence available at the date of the presentation was relevant and took no other scientific evidence into account in reaching its decision. The Appeal Board considered that the slide in question (Slide 13) should be viewed not in isolation, but within the context of the presentation as a whole. In this regard the Appeal Board noted that Slide 11 headed 'Prostamides and Prostaglandins Act at Different Receptors' featured the statement 'Prostamides Act at Their Own Unique Receptors'. Both Slides 12 and 13 listed prostamides as a distinct receptor family to prostaglandins; prostamides appeared in a bold yellow typeface on Slide 13, whereas both cannabinoid and prostaglandin appeared in a white type face as did the adrenergic family receptors, β_1, β_2, a_1 and a_2. The Appeal Board considered the text and design of the slides highlighted prostamides as a distinct receptor family. The Appeal Board considered that a working hypothesis had been presented as scientific fact and the slide in question did not reflect the fact that this was an area of emerging scientific opinion. The Appeal Board considered the slide was misleading and a breach of the Code was ruled.

Pharmacia also alleged that several slides were misleading by the use of suppressed zeros in graphs. The Panel noted that one of the slides comparing Lumigan with Pharmacia's product Xalatan used a suppressed zero; this exaggerated the difference between the products. It was important to consider the immediate visual impression created by the graph. It was irrelevant that intraocular pressure as shown on the slide would not be zero. The graph was misleading and a breach of the Code was ruled.

Pharmacia Limited complained about a presentation given by an employee of Allergan Ltd, which concerned Allergan's product Lumigan (bimatoprost). The presentation had been given at a symposium entitled 'Current Medical and Surgical Treatments for Glaucoma' which had taken place in Edinburgh on 21 September under the sponsorship of the Royal College of Ophthalmology, London. Pharmacia marketed Xalatan (latanoprost).

1 Substantiation

COMPLAINT

Pharmacia stated that the presentation in question was entitled 'Mechanisms of Action of Prostaglandins and Prostanoids'. As Lumigan was the subject this presentation constituted promotion.

Pharmacia submitted that the presentation breached various aspects of the Code and therefore it requested a copy of the slides from Allergan, in accordance with Clause 7.5 of the Code. Allergan declined the request, providing only a list of citations. A repeated request was also declined.

RESPONSE

Allergan denied that it had breached Clause 7.5 which required that a company must provide substantiation of any information, claim or comparison. Intercompany correspondence showed that at no time did Pharmacia specify any information, claim or comparison which it wished to be substantiated but requested the material itself, ie the presentation slides. It seemed clear to Allergan that, by definition, material could not substantiate itself. Allergan considered therefore that its response of sending citations supporting the presentation was in the circumstances more than was required.

PANEL RULING

The Panel noted that Pharmacia had not requested substantiation for any of the information, claims or comparisons contained within slides used in the presentation. Pharmacia had in fact requested copies of the slides themselves and in doing so had referred to the requirement in Clause 7.5 for substantiation to be provided on request and stated that, as promotional claims were made, the presentation was subject to the Code. Allergan did not agree that the matter came within the scope of Clause 7 but nevertheless provided a list of citations supporting the presentation.

The Panel noted that Allergan had sent references to support the presentation. It also noted that Allergan had stated on 6 November that it had no marketing authorization for the product referred to in the presentation.

The Panel did not consider that the failure of Allergan to supply copies of the actual slides to Pharmacia meant that Allergan had failed to substantiate the information, claims or comparisons featured in the slides. No breach of Clause 7.5 of the Code was ruled in this regard.

The Panel noted that in a previous case, Case AUTH/1232/9/01, which concerned the same presentation at the same meeting, it had considered that Lumigan was being promoted prior to the grant of its marketing authorization contrary to the requirements of Clause 3.1 of the Code, a breach of which was accordingly ruled. This ruling had been accepted by Allergan.

2 Emerging scientific opinion

The slide at issue showed the subdivisions of two receptor families. Firstly, 'Lipid Family Receptors' which was subdivided into 'Cannabinoid, 'Prostaglandin' and 'Prostamide'. Secondly, 'Adrenergic Family Receptors' which was subdivided into '$ß_1$', '$ß_2$', 'a_1' and 'a_2'.

COMPLAINT

Pharmacia alleged that slide 18 implied that the concept of 'prostamides' as a distinct group from prostaglandins was an accepted nomenclature, similar to the alpha and beta classification of adrenergic receptors. This was not an established classification, supported by published independent peer-reviewed studies. Pharmacia alleged that this represented a breach of Clause 7.2 of the Code with respect to emerging scientific opinion.

RESPONSE

Allergan stated that it was somewhat confused because Pharmacia alleged breaches of the Code in relation to Slide 18 which did not seem relevant to that particular slide. Slide 13 however compared 'Lipid Family receptors' with the 'Adrenergic Family Receptors'.

The Royal College of Ophthalmology meeting was a meeting of experts in the field of glaucoma and therefore it was perfectly reasonable, and in Allergan's opinion it would be expected, that a scientist would discuss concepts and emerging scientific opinion. This was presented by a named scientist who had been working on prostamides and hypotensive lipids for some 10 years. This emerging opinion had been documented by several authors, for example Woodward *et al* (2001), Cantor (2001) and Brubaker (2001).

PANEL RULING

The Panel noted there was a difference in the numbering of the slides. However, Slide 18 provided by Pharmacia was very similar to Slide 13 referred to by Allergan. The slide provided by Pharmacia was not headed 'Receptor Families' and the layout was slightly different to the slide provide by Allergan. The content complained about was the same. The Panel considered that the impression was given that the lipid family receptors, cannabinoid, prostaglandin and prostamide, were as well established as the $ß_1$, $ß_2$, a_1 and a_2 subdivisions of the adrenergic family receptors. The papers provided by Allergan referred to prostamides as a new class of medicines. The Panel noted that the audience was made up of experts in the field of glaucoma. Such an audience would be familiar with the concepts presented. The Panel decided that in the circumstances the slide was not unreasonable. The issue had been treated in a balanced manner. The Panel ruled no breach of Clause 7.2 of the Code.

APPEAL BY PHARMACIA

Pharmacia alleged that Slide 13 in Allergan's presentation breached Clause 7.2. It suggested that 'prostamides' were distinct from prostaglandins, acting on different target receptors. The wider clinical and scientific community had regarded this theory with some scepticism and Sharif *et al* (2001) stated that: 'contrary to the previous publication (Woodward *et al*, 2001), bimatoprost… binds to and acts as a direct agonist at the …human ocular FP [prostaglandin] receptor'.

Pharmacia submitted that in other words Lumigan exerted its effects in the same way as other prostaglandins. Allergan's slide did not present this alternative view and was not, therefore, balanced.

Pharmacia pointed out that the presentation was given by an Allergan employee, not an independent scientific expert. Further, the references supporting the mode of action described were all authored by, or based upon papers written by, employees of Allergan.

Woodward *et al* (2001)

This article was authored by Allergan staff, and was the first published article to describe bimatoprost as a 'prostamide'.

Brubaker (2001)

This article, which appeared in the same supplement of the journal as Woodward *et al*, stated 'compounds…including bimatoprost have been classified as prostamides'. This statement was

unreferenced. The author then stated that previous studies had demonstrated that bimatoprost had a lack of significant binding affinity to known receptors, and had given 'no good clues as to how this compound might interact with the eye'. The references were to two articles by Woodward.

The first, from Woodward *et al* (2000), stated 'the protein target for (bimatoprost) is unique and is not a known prostanoid (prostaglandin) receptor'. It did not mention the concept of bimatoprost as a 'prostamide', and all authors apart from the last three were Allergan employees.

The second referenced article was again by Woodward and was an abstract presented at the '11th International Conference on Advances in Prostaglandin and Leukotriene Research' 2000. It did not appear on Medline as a published article.

Cantor (2001)

This article stated 'bimatoprost is a synthetic analogue of a newly discovered class of fatty acid amides, called the prostamides'.

Once again, the references to support this statement were to the abstract presented by Woodward at the '11th International Conference on Advances in Prostaglandin and Leukotriene Research' 2000 and to an article by Yu *et al* (1997) which mentioned neither bimatoprost nor prostamides. As stated by Cantor, Yu *et al* had been declared as an advertisement because its publication was partly paid for by the authors.

Thus, the only published original article to state that bimatoprost was a prostamide was authored entirely by Allergan staff.

The article published in the European Journal of Pharmacology 2001 by Sharif *et al*, referred to above, stated that 'contrary to the previous publication (Woodward *et al* 2001), bimatoprost…binds to and acts as a direct agonist at the …human ocular FP receptor'.

In conclusion, any presentation of 'concepts and scientific opinion' should be balanced, reflecting not just the concepts supported by the promoting company. The presentation was not balanced, ignored important alternative views and was therefore in breach of Clause 7.2 of the Code.

COMMENTS FROM ALLERGAN

Allergan considered that Slide 13 was not misleading and not in breach of Clause 7.2 of the Code.

The presentation was delivered at a meeting attended by approximately 70-80 consultant ophthalmologists and doctors with a special interest in the field of glaucoma. The meeting was scientific with the programme covering both medical and surgical treatments for glaucoma.

The presentation was given by an American based employee of Allergan, a pharmacologist and research scientist who had been working on prostamides and hypotensive lipids for some ten years.

The slide originally complained about by Pharmacia was not included in the presentation (and no handouts were given), however a similar slide (Slide 13) was included in the presentation and it was this slide (Slide 13) which had been considered in this case.

The slide was headed 'Receptor Families' and subheaded 'Lipid family receptors' and 'Adrenergic family receptors'; Prostamide was listed within 'Lipid Family Receptors'.

The subject of the presentation was bimatoprost (Lumigan) a new intra-ocular pressure (IOP) – lowering agent which would be marketed by Allergan. Bimatoprost was presented as representing a new class of IOP-lowering agents namely a synthetic prostamide. Publications by Woodward *et al* (2001), Brubaker *et al* (2001) and Cantor (2000) had supported this emerging opinion:

Woodward *et al* (2001)

Allergan stated that the conclusion of this study was that bimatoprost did not exert its effects by stimulating any known major receptor subtype (over 100 receptor types were examined in this study). Woodward summarized that it therefore represented a new generation of IOP lowering drugs.

This article studied the affinity of bimatoprost at an extensive and diverse variety of receptors, ion channels and transporters. It was shown that bimatoprost did not exhibit any meaningful activity at receptors known to include anti-glaucoma drug targets such as prostanoid (DP, $EP_{1\text{-}4}$, FP, IP, TP) or adrenergic ($a_{1\text{-}2}$, $ß_{1\text{-}2}$) receptors. It had however been shown to exhibit potent pharmacological activity in the feline iris sphincter preparation which was prostamide sensitive.

Pharmacia criticised this article because it was authored by Allergan staff and therefore considered that it could not be independent. However it was often the case that when a pharmaceutical company developed a novel compound then the initial publications were by the scientists who were involved in the research; additionally the article was subjected to peer review.

Brubaker *et al* (2001)

Allergan stated that this article attempted to summarize the major points of a previous study of bimatoprost's mechanism of action and discussed the implications of the findings of this study. The quotes from this article referred to in Pharmacia's letter were out of context.

The first quote in Brubaker's introduction was: 'Compounds closely related to prostamide F, including bimatoprost, have been classified as prostamides'. The meaning was changed when words were omitted from this sentence as they were in Pharmacia's appeal.

The second quote from this introductory paragraph went on to explain that the binding affinity of bimatoprost at known receptors was examined in order to establish a mechanism of action.

Pharmacia again considered that this was not independent as the statements related to prostamide

were referenced to Woodward, an Allergan author. Dr Brubaker however was an independent ophthalmologist who was very highly regarded. Although he had acted as a consultant for Allergan he had also consulted for other companies and he had no proprietary interest in bimatoprost or any other product for glaucoma. Indeed, a few years ago, Brubaker had conducted the same study on latanoprost and, like bimatoprost, Brubaker published an article on latanoprost's mechanism of action. For Pharmacia to now claim that Allergan could not rely on the Brubaker article was disingenuous. The Brubaker paper was also peer reviewed and could therefore be considered as an independent review.

Cantor (2001)

This peer reviewed review was by a highly regarded ophthalmologist who had acted as a principal investigator for Pharmacia clinical trials pursuant to grants funded by Pharmacia. In addition, Cantor had spoken on behalf of another pharmaceutical company in the last year and had consulted for others.

The quote from this paper to which Pharmacia referred ie 'bimatoprost is a synthetic analogue of a newly discovered class of fatty acid amides, called prostamides' was intended to demonstrate the existence of a COX-2 mediated biosynthetic pathway for the production of a novel class of compound from anandamide. It was not an attempt to describe the affinity of bimatoprost for ligand receptor sites, this was in Table 1 of Cantor's review.

Sharif *et al* (2001)

Allergan stated that this article was published in December 2001 ie several months after the presentation at issue and this was not therefore part of the body of data available at the time.

It was in Allergan's opinion misleading firstly because an article by Woodward was cited and discussed but the authors had omitted substantive information. Notably, the fact that bimatoprost did exhibit marked potency in certain pharmacological preparations was not mentioned ie EC_{50} = 34 nM in the feline iris sphincter (Kraus *et al* 1999). The EC_{50} represented the plasma concentration/AUC required for obtaining 50% of the maximum effect *in vivo*. This was very important as it demonstrated that bimatoprost was a potent pharmacophore and this greatly assisted in explaining its highly efficacious ocular hypotensive effects.

Secondly, Sharif attributed significance to the pharmacologically meaningless affinity of bimatoprost for the FP receptor K_i= 6310 nM. K_i was the concentration of the ligand that would bind to half the binding sites at equilibrium, if K_i was low the affinity for the receptor was high. In previous articles on its newly marketed drug fluprostenol 1-isopropyl ester (Travatan), the Alcon research group had adopted a different position on such findings. They reported a K_i value for fluprostenol at the FP receptor of 52.2 nM and K_i values at EP_3 and EP_1 receptors of 3501 and 9540, respectively. These findings were interpreted as (i) 'selective FP prostaglandin agonist' (Hellberg *et al* Oct 2001) (ii) 'no meaningful affinity or activity at other receptors' (Netland *et al* Oct 2001). The K_i value of 6310nM was between K_i 3501nM and 9540nM and therefore bimatoprost did not have meaningful affinity or activity at the FP receptor.

Thirdly, the study was not adequately controlled. The purported FP antagonist used in this study (AL-8810) was actually a partial agonist (Griffin *et al* 1999). This was not mentioned and appropriate control data was not provided. In the absence of such information, the reader was uncertain whether the attenuation caused by AL-8810 was attributable to receptor occupation or resulted from partial release of a common $[Ca^{2+}]$ store. It was important that data clearly showed the effects of AL-8810, *per se*, on $[Ca^{2+}]_i$. If AL-8810 released $[Ca^{2+}]_i$, then its ability to block the effects of bimatoprost should be compared to its effects against other agents capable of releasing $[Ca^{2+}]_i$.

Finally, the authors of this article were from Alcon Research Ltd; Alcon was a pharmaceutical company also in the field of glaucoma. The logical extension of Pharmacia's argument was that this article must be viewed as being of the same level of independence as the articles published by Allergan staff.

Lumigan US prescribing information

The mechanism of action section of the US prescribing information, which was approved by the FDA approximately 6 months before the presentation at issue, reflected the unique nature of bimatoprost as a prostamide. It stated 'Bimatoprost is a prostamide, a synthetic structural analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides'.

The draft summary of product characteristics (SPC) for the UK that had received a positive CPMP opinion, contained similar wording but to date the product had not received a marketing authorisation.

In conclusion Allergan considered that the data which was presented summarized the views of both Allergan scientists and independent experts. It was a comprehensive, accurate and balanced presentation of the emerging scientific opinion. The presentation could not include comments on an article which was published after the presentation. Allergan considered that Slide 13, in the context in which it was shown, was not misleading and not in breach of the Code.

FURTHER COMMENTS FROM PHARMACIA

It remained Pharmacia's contention that Slide 13 was in breach of Clause 7.2 of the Code by describing 'prostamide' receptors as a distinct class apart from prostaglandins.

The prostaglandin analogue group of anti-glaucoma drugs were prodrugs. In other words, the drugs as administered were not active, but were converted to an active form in the body. It was this active form which then affected the target receptor.

Pharmacia stated that bimatoprost was converted *in vivo* to its active form, the free acid of the parent compound, and therefore had the same mode of action as latanoprost and travoprost. It did not

represent the first of a new chemical class and did not have a unique mode of action at the 'prostamide' receptor, which to date had not been shown to exist by independent researchers or characterized in scientific literature.

The slide

Pharmacia stated that by showing 'prostamide' as a receptor family alongside the accepted receptor families of prostaglandin, adrenergic, etc, the slide was misleading. To date, only one citation containing the word 'prostamide' was found in a Medline search of the published medical literature from 1966-2002 March (Woodward *et al* 2001). All references made to 'prostamide' referred to Allergan-created, or Allergan-sponsored, material.

Pharmacia concluded that prostamide receptors had not been characterized or described in the scientific literature. Therefore the slide in question was unbalanced because it showed prostamides as a distinct family of lipid receptors.

The speaker

The speaker was an Allergan employee, not an independent researcher. A Medline search from 1966-2001 identified 18 articles in which the speaker had authored or co-authored, including the one prostamide article (a review). He had worked on bimatoprost only in his capacity as an Allergan employee. At the 2001 International Glaucoma Symposium in Prague, he had stated during a presentation involving bimatoprost that, 'If bimatoprost is a prodrug, then it is a prostaglandin'.

Woodward *et al* (2001)

While Woodward demonstrated that bimatoprost was not active on more than 100 receptors tested, that did not provide evidence for a new drug class or an undiscovered drug receptor. On the contrary, a reasonable conclusion was that bimatoprost acted as a prodrug like the other prostaglandin analogs, latanoprost and travoprost. A prodrug was not active until it was converted to its active form; in the case of the prostaglandins, the active form was the acid of the parent compound (ie acid of latanoprost).

As demonstrated by Maxey *et al* (2002) and Sharif (2001) bimatoprost was a prodrug which was not expected to act on the 100 receptors, just as the other prostaglandin pro-drugs latanoprost and travoprost (other well-accepted members of the prostaglandin class) did not show meaningful activity on these 100 receptors. Only their active metabolite (free acid form) was active on prostaglandin receptors.

Concerning the feline iris sphincter model which was said to be prostamide sensitive, the reference cited (Krauss *et al*) was published in 1999 and the word 'prostamide' was never used in the published abstract or presented poster. As the author stated in the first sentence of the poster abstract, the feline iris sphincter model was established as a prostaglandin F receptor preparation. It was a well known and accepted surrogate marker to test for prostaglandin activity and was frequently used during the discovery of the other prostaglandin compounds. That bimatoprost demonstrated activity in the feline iris sphincter model suggested that bimatoprost was converted *in vitro* to its active acid form which in turn produced the positive response. However, that reasonable explanation was not addressed in the publication; again no fair balance in the medical literature.

As the feline iris sphincter was a model for prostaglandin activity, conversion of bimatoprost to the active form which acted on prostaglandin receptors was a reasonable explanation that was not provided.

Allergan noted in its response that initial publications for novel compounds were authored by the scientists involved in the research. However, it was quite unusual for a pharmaceutical company to withhold the identification or structure of a new molecular entity until it was approved by regulatory authorities, as was the case with bimatoprost in March 2001. This was particularly extraordinary for a compound purported to be the first in a new drug class. In fact, only one clinical study was published in the scientific literature prior to the medicine's approval (Brubaker *et al* 2001). In contrast, the development of prostaglandins, and latanoprost in particular, was well documented in the medical literature by scientists working for the pharmaceutical industry and independent researchers in academia.

Without knowing the composition of a compound, it was impossible for researchers to independently confirm or refute scientific findings or claims. In the case of bimatoprost, independent research of the drug's actions could not begin until March 2001 when the scientific community learned of its chemical structure. Nevertheless, in less than a year of learning bimatoprost's chemical structure, two separate laboratories had published their independent findings demonstrating that bimatoprost was indeed a prodrug with an active acid metabolite, and, in one of the studies, the acid of bimatoprost had demonstrated potent activity on the prostaglandin F receptor (Sharif *et al* 2001). Importantly, no independent researcher had identified the purported 'prostamide' receptor nor had any independent scientists been able to confirm Allergan's claim that bimatoprost was not a prodrug whose actions were not related to activity on the prostaglandin F receptor.

Brubaker (2001)

Pharmacia agreed that Brubaker was a highly regarded ophthalmologist whose work was valued by the scientific community. Nevertheless, Brubaker relied upon information provided by Allergan concerning prostamides and the statements in the paper concerning prostamides were based on research conducted by Allergan, not Brubaker. Regardless, Brubaker had published two papers concerning bimatoprost's mechanism of action; one was the results from his original research and the other a review of the former. In both papers, Brubaker's conclusions regarding bimatoprost's mechanism of action suggested that its actions were similar to that of latanoprost. It would be reasonable to consider therefore, that bimatoprost's action was mediated via the same prostaglandin receptor as latanoprost to achieve its therapeutic effect.

Cantor (2001)

Contrary to Allergan's statement Cantor had never worked as a principal investigator for Pharmacia. Pharmacia referred to the previous points made concerning Table 1 of this reference.

Sharif (2001)

As previously discussed, because the structure of bimatoprost was not made available to the scientific community prior to March 2001, the findings of Sharif (and now Maxey) now confirmed what was suspected concerning the acid of bimatoprost's actions on the prostaglandin receptor. Pharmacia agreed with Allergan's assertion that bimatoprost did not have meaningful affinity or activity at the FP receptor.

As Sharif demonstrated, it was the acid of bimatoprost that imparted a similar potent activity on the prostaglandin F receptor as the acid of travoprost. Sharif used travoprost acid (the active form of travoprost), a known prostaglandin receptor agonist, to serve as the control for bimatoprost and its active acid. Similarly Maxey demonstrated that bimatoprost was converted in human eye tissue to its free acid which was identical to the free acid of latanoprost (with the exception of a double bond). To serve as appropriate controls, Maxey used the parent and active acid forms of three other known prostaglandin receptor agonists (latanoprost, travoprost, and unoprostone).

Regardless of Sharif's affiliation, his work represented the first independent research that attempted to confirm or refute Allergan's claim that bimatoprost did not act on prostaglandin receptors. Separately, Maxey's independent work further elucidated bimatoprost's probable mechanism of therapeutic activity that was consistent with the findings of Sharif, that bimatoprost was prodrug that required conversion in the eye to its free acid which was active on prostaglandin F receptors.

Lumigan US prescribing information

For the purpose of reviewing Allergan's actions in the UK, the relevance of bimatoprost's labelling in the US was unclear. While the FDA was not charged with the responsibility for naming drug compounds, the FDA did insist that bimatoprost was identified as a structural analog of prostaglandin in its labelling. In the absence of data to suggest otherwise, the FDA accepted Allergan's assertion concerning bimatoprost and prostamides. Regardless of the US labelling, the compelling scientific evidence available today indicated that bimatoprost did in fact act as a prodrug that was converted to an active acid form which acted on prostaglandin F receptors. Further, action on the prostaglandin F receptor was likely responsible for its therapeutic activity, as believed to be the case for other prostaglandin compounds.

Importantly, other US pharmaceutical authorities, such as the Compendia publication, Drug Facts & Comparisons, had also evaluated bimatoprost and had classified it as a prostaglandin agonist, listing it among the other prostaglandin agents latanoprost, travoprost and unoprostone.

If considering the US Lumigan (bimatoprost) labelling, Pharmacia submitted it might be useful to compare it to the US labelling of Xalatan (latanoprost) and Travatan (travoprost), drugs that had been accepted to act on prostaglandin receptors. It was remarkable that bimatoprost had the same unique characteristics that had, to date, only been associated with these other prostaglandin compounds.

In summary, the slide in question was misleading because prostamide receptors were not an established class as the other receptors classes shown in the same slide. The existence of prostamides or prostamide receptors was not a generally accepted viewpoint.

APPEAL BOARD RULING

The Appeal Board noted that the presentation at issue took place at a medical symposium on 21 September 2001; the audience comprised experts in the field of glaucoma. The Appeal Board considered that only scientific evidence available at the date of the presentation was relevant and took no other scientific evidence into account when reaching its decision.

The Appeal Board noted the discussion of, and reference to, receptor subtypes in Woodward *et al* (2001), Brubaker (2001) and Cantor (2001), all of these papers had been published prior to the presentation at issue. At the appeal hearing the Allergan representatives stated that they had no knowledge of the Sharif *et al* data prior to its publication in December 2001.

At the time of the meeting in question the product was available in the US. The labelling in the US described bimatoprost as 'a prostamide, a synthetic structural analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides'. It was established at the appeal hearing that Lumigan received a UK marketing authorization on 8 March 2002, and that the structure of Lumigan had been made public in March 2001.

The Appeal Board noted that at the appeal hearing Allergan had stated that the presentation of a prostamide receptor as a distinct receptor family represented a reasonable working hypothesis. It was further stated that Allergan was not attempting to say there was no debate. Allergan considered that in September 2001 the presentation represented the balance of that debate. The Appeal Board noted that Allergan had stated that the prostamide receptor had not been identified and there was no prostamide receptor model that could be used. Further, the possibility that bimatoprost was a prodrug had been anticipated by Allergan scientists and Allergan's view was that the issue had been satisfactorily addressed by Woodward *et al*. That study showed that in human iris-ciliary body tissue homogenates there was no conversion of bimatoprost to bimatoprost free acid metabolite after 3 hours.

The Appeal Board considered that Slide 13 should be viewed not in isolation, but within the context of the presentation as a whole. In this regard the Appeal Board noted that Slide 11 headed 'Prostamides and Prostaglandins Act at Different Receptors' featured

the statement 'Prostamides Act at Their Own Unique Receptors.' Both Slides 12 and 13 listed prostamides as a distinct receptor family to prostaglandins; prostamides appeared in a bold yellow typeface on Slide 13, whereas both cannabinoid and prostaglandin appeared in a white type face as did the adrenergic family receptors, B_1, B_2, a_1 and a_2. The Appeal Board considered the text and design of the slides highlighted prostamides as a distinct receptor family. The Appeal Board considered that a working hypothesis had been presented as scientific fact and the slide in question did not reflect the fact that this was an area of emerging scientific opinion. The Appeal Board considered the slide was misleading; a breach of Clause 7.2 was ruled. The appeal on this point was successful.

In reaching its decision the Appeal Board took no account of the additional studies provided by Pharmacia when commenting upon Allergan's response to the appeal and nor did it consider additional data not previously seen by Allergan which appeared in Pharmacia's presentation at the appeal hearing.

3 Suppressed zeros

COMPLAINT

Pharmacia stated that several slides were misleading by use of suppressed zeros. For example, Slide 64 showing the diurnal intraocular pressure (IOP) at month 3 in a study of Lumigan and Xalatan contained a graph that had a suppressed zero on the x-axis with the scale starting instead at 16mmHg and finishing at 19mmHg.

Pharmacia alleged that the graphs were in breach of Clause 7.8 of the Code, by misleading use of scale.

A similar allegation was made in relation to Slide 62. A further allegation was also made about Slide 62.

RESPONSE

Allergan stated that the Authority had been provided with all of the slides shown at the meeting. The slides provided by Pharmacia were not shown at the meeting. However Allergan acknowledged that Slides 16 and 19 contained suppressed zeros.

Allergan stated that it was fully committed to abiding by the Code and it invested considerable time and resource to ensure that all promotional activities complied with it. Allergan therefore apologised unreservedly for any unintentional breaches of the Code. It had taken steps to reinforce to its Global Research and Development colleagues that any activity within the UK, whether of a scientific or promotional nature, must comply fully with the requirements of the Code.

PANEL RULING

The Panel noted that Slide 62 referred to by Pharmacia had not been used in the presentation. None of the slides provided by Allergan showed the same data as Slide 62. The Director decided that there was no *prima facie* case to answer in respect of the slide referred to by Pharmacia as Slide 62.

The Panel noted that Slide 64 headed 'Diurnal IOP Control at Month 3' referred to by Pharmacia was very similar to Slide 19 provided by Allergan. Both used suppressed zeros and compared Xalatan with Lumigan with regard to mean IOP at 8am, 12 noon, 4pm and 8pm. The colours and symbols used for the two products were different but the content was very similar. The graphs showed that Lumigan lowered IOP to a greater extent than Xalatan at 12 noon and 4pm ($p \leq 0.05$). The Panel noted that slide 19 (Allergan numbering) used a suppressed zero; this exaggerated the difference between Lumigan and Xalatan. It was important to consider the immediate visual impression created by the graph. It was irrelevant that IOP would not be zero. The graph was misleading. The Panel therefore ruled a breach of Clause 7.8 of the Code.

Complaint received **30 November 2001**

Case completed **19 June 2002**

CASE AUTH/1262/12/01

BRISTOL-MYERS SQUIBB and SANOFI-SYNTHELABO v MERCK SHARP & DOHME

Promotion of Cozaar

Bristol-Myers Squibb and Sanofi-Synthelabo complained about Merck Sharp & Dohme's use of the RENAAL study results to promote Cozaar (losartan). The RENAAL study looked at the effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetics with nephropathy. 1513 patients were enrolled in the randomized, double blind study comparing losartan (50mg to 100mg once daily) with placebo, both taken in addition to conventional antihypertensive treatment (other than ACE inhibitors or AII antagonists) for a mean of 3.4 years. Patients were not allowed to take ACE inhibitors or AII antagonists. The primary outcome was the composite of a doubling of the baseline serum creatinine concentration, end stage renal disease or death. Secondary endpoints included a composite of morbidity and mortality from cardiovascular causes, proteinuria and the rate of progression of renal disease. Losartan reduced the incidence of a doubling of the serum creatinine concentration and endstage renal disease but had no effect on the rate of death. The benefit exceeded that attributable to changes in blood pressure. The composite of morbidity and mortality from cardiovascular causes was similar in the two groups. The study concluded that losartan led to significant improvement in renal outcomes that was beyond that attributable to blood pressure control in patients with type 2 diabetes and nephropathy.

A four page report headed 'A report from The American Society of Hypertension Meeting' gave the results of the RENAAL study which were presented for the first time at the meeting. Bristol-Myers Squibb and Sanofi-Synthelabo stated that the results suggested that losartan delayed the progression of diabetic nephropathy, reduced proteinuria, and reduced the risk of hospitalization for heart failure in patients with type 2 diabetes. Cozaar was only licensed for the treatment of essential hypertension and therefore the report promoted losartan for uses that fell outside the marketing authorization. Bristol-Myers Squibb and Sanofi-Synthelabo disagreed with Merck Sharp & Dohme's view that, as the majority of patients in the study were hypertensive (94%), the promotion of the data fell within the licensed indication. A breach of the Code was alleged.

Bristol-Myers Squibb and Sanofi-Synthelabo were concerned that if the report was delivered to health professionals who did not attend the meeting, it could be viewed as a breach of the Code for the reasons mentioned above.

The Panel noted that the meeting report had been used in the UK to convey the results of the RENAAL study to doctors. It had been presented as promotional material. Prescribing information had been included. The report had been used by the representatives. The report clearly referred to the results of the study in the context of hypertensive patients.

The Panel noted that the Cozaar summary of product characteristics (SPC) stated that it was indicated for the treatment of hypertension. It was not indicated for heart failure. There was no mention in the SPC of its use in type 2 diabetics as a separate indication. Cozaar could be used in patients with hypertension who were also type 2 diabetics. The SPC stated that Cozaar could be administered with other antihypertensive agents and that the concomitant use of Cozaar with ACE inhibitors had not been adequately studied. Reference was also made to use in renal and hepatic impairment.

In the Panel's view, given that 97% of patients in the study were diagnosed as hypertensives, that both the baseline blood pressure figure, 150/82mmHg, and the target figure in the study of less than 140/90mmHg were above the target for the population currently set by the British Hypertension Society (140/80mmHg), the study population could be considered as being a hypertensive population. The Panel did not consider that the report promoted Cozaar to delay the progression of diabetic nephropathy, reduce proteinuria in type 2 diabetes or heart failure *per se*. The outcomes were presented in the context of treating hypertension. No breach of the Code was ruled in this regard. The Panel also ruled no breach with regard to the allegation that delivering the report to health professionals who had not attended the meeting in effect promoted Cozaar outside the marketing authorization. Both of these rulings were appealed.

Upon appeal the Appeal Board was concerned that the material at issue used claims such as 'Proven renal protection', 'Clinical benefits of Cozaar in RENAAL were due to effects beyond blood pressure lowering' and 'results that demonstrate renal protection'. The Appeal Board noted that Cozaar was not licensed for renal protection; its only licensed indication was to lower blood pressure. In the Appeal Board's view the renoprotective effects had been given undue emphasis and had not been placed sufficiently within the context of treating hypertension such that the material appeared to promote Cozaar for its renoprotective effect.

The report had been used by Merck Sharp & Dohme's representatives and had been distributed to health professionals who had not attended the meeting. The Appeal Board noted its comments above and considered that the report promoted Cozaar beyond the terms of the marketing authorization and was inconsistent with its SPC. Any use of the report was therefore inappropriate. Breaches of the Code were ruled.

Bristol-Myers Squibb and Sanofi-Synthelabo stated that the meeting report did not represent a balanced, fair and objective evaluation of all the evidence. The meeting had three other oral presentations using AII antagonists to treat type 2 diabetics with renal disease, two of which were in the same scientific session. Only a brief mention was given to one of these studies.

The Panel considered that the report was very clear that it covered the results of the RENAAL study. Readers would not expect it to be a report of the whole meeting nor of the whole scientific session. The Panel did not consider there was a breach of the Code as alleged. This ruling was not appealed.

Bristol-Myers Squibb and Sanofi-Synthelabo also alleged that the promotional item was disguised as a meeting report. The Panel did not consider that readers would be misled into thinking that the report was anything other than promotional material. It was provided by representatives and prescribing information was included. The Panel ruled no breach of the Code. This ruling was not appealed.

Bristol-Myers Squibb and Sanofi-Synthelabo alleged that the report failed to declare that the meeting was sponsored.

The American Society of Hypertension meeting had not been sponsored by Merck Sharp & Dohme. The Panel therefore ruled no breach of the Code. This ruling was not appealed.

Bristol-Myers Squibb and Sanofi-Synthelabo also complained about an exhibition panel and a leavepiece. The exhibition panel was headed 'Results. Proven renal protection' followed by 'Helping you protect your hypertensive type II diabetic patients from dialysis and transplantation'. The claims were referenced to the RENAAL study. The results of the study were given.

The six page leavepiece was headed 'Announcing landmark trial results' and one page referred to the demonstrated renal protection in the RENAAL study referring to '… landmark results in hypertensive type II diabetics'.

Bristol-Myers Squibb and Sanofi-Synthelabo were concerned that the material was being used by Merck Sharp & Dohme representatives at company sponsored meetings. They considered that the study was not evaluating the effects of blood pressure reduction and as such the exhibition panel and leavepiece promoted Cozaar outside its licensed indication; the existence of the leavepiece demonstrated that Merck Sharp & Dohme was encouraging representatives to proactively discuss the RENAAL study results.

On balance the Panel considered that the exhibition panel and the leavepiece were not inconsistent with the Cozaar SPC. The product was clearly being promoted for the treatment of hypertension. The renal outcomes were presented as benefits to using losartan for blood pressure control. The Panel therefore ruled no breach of the Code on this point. This ruling was appealed.

Upon appeal the Appeal Board noted its comments above. The exhibition panel was headed 'Results. Proven renal protection' and sub-headed 'Helping you protect your hypertensive type II diabetic patients from dialysis and transplantation'. Although the terms 'anti-hypertensive' and 'hypertensive type II diabetic' had been used within the body of the panel the Appeal Board's view was that it had not been made clear that the reason to prescribe Cozaar was for the treatment of hypertension. Similarly the relevant sections of the leavepiece emphasised the renal effects of Cozaar without making it clear that it must be prescribed to lower blood pressure. A breach of the Code was ruled.

Bristol-Myers Squibb and Sanofi-Synthelabo also expressed concerns that reprints of the RENAAL article from the New England Journal of Medicine were being distributed without prescribing information unsolicited by Merck Sharp & Dohme representatives from stands at these meetings.

The Panel did not consider that the report had been provided unsolicited, as meant by the clause cited, making it available on the company stand was in effect soliciting such requests. Representatives had been providing it on request. It had been used as a reference in promotional material. The Panel therefore ruled no breach of the Code. This ruling was not appealed.

The Panel considered that Merck Sharp & Dohme was using the published study for a promotional purpose. Such use had to comply with the Code. The Panel noted that Merck Sharp & Dohme's materials clearly set the results in the context of treating hypertension and on balance the Panel did not consider that use of the published paper meant that Merck Sharp & Dohme was promoting outside the licensed indications as alleged. The Panel therefore ruled no breach of the Code in this regard. This ruling was appealed.

With regard to the representatives' use of the RENAAL reprints, the Appeal Board noted Merck Sharp & Dohme's original response that these were handed out if requested. The Appeal Board considered that making the reprints available in response to a specific request (ie using the paper reactively not proactively) was acceptable and upheld the Panel's ruling of no breach.

Bristol-Myers Squibb and Sanofi-Synthelabo also alleged that a four page leavepiece provided further evidence that Merck Sharp & Dohme's representatives were promoting Cozaar for a use outside the marketing authorization. The leavepiece stated 'Helping you protect your hypertensive type II diabetic patients from dialysis and transplantation', 'RENAAL proves COZAAR can help protect the kidneys of your hypertensive type II diabetic patients' and 'The first time any antihypertensive has been shown in hypertensive type II diabetics to significantly reduce the need for dialysis and transplantation'.

The Panel noted its rulings above. The leavepiece now at issue clearly referred to hypertensive type 2 diabetic patients. The Panel considered that on balance the leavepiece was not inconsistent with the Cozaar SPC. The product was clearly being promoted for the treatment of hypertension. The renal outcomes were presented as benefits to using losartan for blood pressure control. The Panel therefore ruled no breach of the Code. This ruling was appealed.

With regard to the four page leavepiece the Appeal Board noted its comments about the exhibition

panel and the six page leavepiece and ruled a breach of the Code.

Bristol-Myers Squibb and Sanofi-Synthelabo alleged that by actively promoting Cozaar for an unlicensed indication, Merck Sharp & Dohme's activities could reduce confidence in and bring discredit upon the industry.

The Panel noted its rulings of no breach above. It did not consider that there had been a breach of Clause 2 of the Code and ruled accordingly. This ruling was not appealed.

Bristol-Myers Squibb Pharmaceuticals Limited and Sanofi-Synthelabo Limited complained about the promotion of Cozaar (losartan) by Merck Sharp & Dohme Limited. Cozaar was an angiotensin-II (AII) antagonist indicated for the treatment of hypertension.

Bristol-Myers Squibb and Sanofi-Synthelabo stated that the basis of the dispute related to the promotion of the RENAAL trial results which were presented at the American Society of Hypertension Meeting in May 2001 and were published in the New England Journal of Medicine on 20 September 2001 (Brenner *et al*).

The RENAAL study looked at the effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. A total of 1513 patients were enrolled in the randomized, double-blind study comparing losartan (50mg to 100mg once daily) with placebo, both taken in addition to conventional antihypertensive treatment (calcium channel antagonists, diuretics, alpha-blockers, beta-blockers and centrally acting agents) for a mean of 3.4 years. Patients were not allowed to take ACE inhibitors or AII antagonists. The primary outcome was the composite of a doubling of the baseline serum creatinine concentration, end stage renal disease or death. Secondary endpoints included a composite of morbidity and mortality from cardiovascular causes, proteinuria and the rate of progression of renal disease. Losartan reduced the incidence of a doubling of the serum creatinine concentration (risk reduction, 25%; p=0.006) and endstage renal disease (risk reduction, 28%; p=0.002) but had no effect on the rate of death. The benefit exceeded that attributable to changes in blood pressure. The composite of morbidity and mortality from cardiovascular causes was similar in the two groups, although the rate of first hospitalization for heart failure was significantly lower with losartan (risk reduction, 32%; p=0.005). The level of proteinuria decreased by 35% with losartan (p<0.001 for the comparison with placebo). The study concluded that losartan led to significant improvement in renal outcomes that was beyond that attributable to blood pressure control in patients with type 2 diabetes and nephropathy.

Bristol-Myers Squibb and Sanofi-Synthelabo stated that the main disagreement centred around whether promoting these renal benefits for Cozaar was consistent with the licensed indication for the treatment of hypertension. The observed effects were independent of blood pressure lowering.

Merck Sharp & Dohme provided background information in relation to whether the RENAAL study was within the current Cozaar marketing authorization.

Merck Sharp & Dohme stated that RENAAL was a study in patients with type 2 diabetes and advanced diabetic nephropathy, indicated by marked protein loss in the urine. Inherent in this condition was a tendency for blood pressure to be elevated, and central to treatment was the control of blood pressure. Merck Sharp & Dohme's opinion was that to dissociate the lowering of blood pressure from the renal outcomes in RENAAL was contrived, inconsistent with the study itself and with current opinion.

In the RENAAL design paper it was clear that patients received losartan or placebo, in addition to 'other antihypertensive therapy', indicating that losartan was being used as an antihypertensive agent. The final dose of losartan used in the study was dependent on the blood pressure response, with the dose being increased to 100mg if blood pressure remained elevated.

Current opinion also indicated that patients such as those in RENAAL were in need of antihypertensive treatment. Blood pressure treatment thresholds and targets for diabetic patients were lower than for the population as a whole and indeed it was not even possible to define hypertension in terms of a single blood pressure figure alone. Current guidelines advised that treatment thresholds were based on overall cardiovascular risk, which was extremely high in this group of patients (about 34% over 4 years). For example The Royal College of Physicians Series 'Horizons in Medicine', a series summarising the current knowledge, stated that 'It is now widely accepted that early and aggressive treatment of arterial hypertension is an important goal in the management of diabetic nephropathy …'. Similarly, the Oxford text book of Nephrology indicated that '… in type II diabetics, hypertension usually precedes the onset of diabetes mellitus by several years'.

Merck Sharp & Dohme submitted that to try to dissociate diabetic nephropathy from hypertension was simply not possible. All patients with this degree of diabetic nephropathy were considered hypertensive, and in need of antihypertensive medication.

Merck Sharp & Dohme pointed out that it was important to note that the vast majority (97%) of the patient population recruited into RENAAL already had a diagnosis of hypertension and most (94%) were on some form of antihypertensive treatment. A very few (3%) were not considered hypertensive at the time the study was started (1996) but would be by today's standards. Despite being on background treatment, the baseline blood pressure for the group as a whole was 152/82 which was still above the targets set for this population (140/80 in the British Hypertension Society guidelines). On all of the baseline criteria therefore, this was a cohort of partially treated hypertensive type 2 diabetic patients with proteinuria.

The hypothesis being tested was that control of blood pressure with a losartan-based treatment strategy (blocking the renin-angiotensin-aldosterone system,

RAAS) would have advantages over controlling the blood pressure with non-RAAS agents. The dose of study medicine was increased (or additional treatment added) based on whether the blood pressure was controlled and not on any diabetic or renal parameter such as changes in proteinuria or creatinine.

Further evidence of the centrality of blood pressure control to the study was shown in newsletters which were issued from time to time to investigators. These clearly showed that investigators were asked to adjust study medication diligently, based on blood pressure response.

In summary, RENAAL was a population of diabetic patients who required blood pressure reduction in whom this was provided in two forms – with and without losartan. It represented a sub-group of the current licence which was 'for the treatment of hypertension'.

Based on this rationale, Merck Sharp & Dohme had been promoting the RENAAL results through its representatives with the use of reprints, detail aids, exhibition panels, etc. It had been explicit in its materials, and when briefing representatives, that the promotion of Cozaar was strictly limited to patients who required blood pressure reduction, and that losartan was not indicated for the treatment of diabetes or for the treatment of diabetic nephropathy *per se*.

A Report from the American Society of Hypertension Meeting

The four page report (ref 08-02 CZR.01.GB.10281.L.7.10m.CW.0701) was headed 'A report from The American Society of Hypertension Meeting'. It gave the results of the RENAAL study which were presented for the first time at the meeting. Prescribing information for Cozaar was included on page 4.

1 Alleged promotion outside the marketing authorization

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo stated that the results suggested that losartan delayed the progression of diabetic nephropathy, reduced proteinuria, and reduced the risk of hospitalization for heart failure in patients with type 2 diabetes. Cozaar was only licensed for the treatment of essential hypertension and therefore the report promoted losartan for uses that fell outside the marketing authorization.

Bristol-Myers Squibb and Sanofi-Synthelabo disagreed with Merck Sharp & Dohme's view that, as the majority of patients within this trial were hypertensive (94%), the promotion of the data fell within the licensed indication. A breach of Clause 3.2 was alleged.

Bristol-Myers Squibb and Sanofi-Synthelabo were concerned that if the report was delivered to health professionals who did not attend the meeting, it could be viewed as a breach of Clause 3.2 for the reasons mentioned above.

RESPONSE

Merck Sharp & Dohme stated that the report was produced to convey to doctors the important new data that were presented orally at the American Society of Hypertension Meeting. The results were accepted for presentation at an international hypertension conference, not at a diabetic or renal conference. The results were certainly newsworthy and were covered by both medical and non-medical press. Since the results were announced at a 'Hot-Line' session for recently available data, no written abstract was available. Merck Sharp & Dohme therefore used this report of the results, as they were presented, whilst awaiting full reprints from the New England Journal of Medicine. It was no longer being used by the representatives having been replaced by the published paper.

Bristol-Myers Squibb and Sanofi-Synthelabo stated that the report suggested that losartan delayed the progression of diabetic nephropathy, reduced proteinuria and reduced the risk of hospitalization for heart failure. This was correct. However, as indicated above, losartan did so in a group of patients who had hypertension as well as (and indeed, possibly as part of) diabetic nephropathy and were therefore within the scope of the current marketing authorization.

Merck Sharp & Dohme stated that the report was based on the oral presentation at the meeting. It was written as a complete report of all of the data presented relating to RENAAL. It included both the renal and cardiovascular outcomes (the primary and secondary endpoints of the study) as they were presented. Merck Sharp & Dohme was very conscious that losartan did not have a licence for the treatment of heart failure, but to have omitted these aspects of the presentation would have resulted in an incomplete report, not reflecting all of the RENAAL data presented at the meeting.

Merck Sharp & Dohme stated that it had not been promoting for the treatment of diabetic nephropathy or for the treatment heart failure, but the results of RENAAL indicated that these benefits might reasonably be expected as a consequence of treating a hypertensive diabetic cohort with losartan.

PANEL RULING

The Panel noted that the meeting report had been used in the UK to convey the results of the RENAAL study to doctors. It had been presented as promotional material. Prescribing information had been included. The report had been used by the representatives. The report clearly referred to the results of the study in the context of hypertensive patients.

The Panel noted that the Cozaar summary of product characteristics (SPC) stated that it was indicated for the treatment of hypertension. It was not indicated for heart failure. There was no mention in the SPC of its use in type 2 diabetics as a separate indication. Cozaar could be used in patients with hypertension who were also type 2 diabetics. The SPC stated that Cozaar could be administered with other antihypertensive agents and that the concomitant use of Cozaar with ACE inhibitors had not been

adequately studied. Reference was also made to use in renal and hepatic impairment.

Patients in the RENAAL study had to have been diagnosed with type 2 diabetes and nephropathy. The Panel noted Merck Sharp & Dohme's submission that 97% of patients also had a diagnosis of hypertension, 94% were on some form of treatment and that the 3% who were not considered hypertensive at the time of the start of the study (1996) would be by today's standards. The study report stated that 92.3% of patients in the losartan group and 94.6% of patients in the placebo group were receiving antihypertensive therapy at baseline. The Panel had some sympathy with Merck Sharp & Dohme's submission that on the baseline criteria this was a cohort of partially treated hypertensive type 2 diabetic patients with proteinuria.

The Panel noted that it had not been demonstrated that 100% of the patients in RENAAL had hypertension. A few, albeit a small minority (3%), were not diagnosed as having hypertension. The Panel noted Merck Sharp & Dohme's submission that the average baseline blood pressure figures of 150/82mmHg were above the targets of 140/80mmHg set for this population by the British Hypertension Society. The RENAAL study did not investigate Cozaar for lowering blood pressure. This had of course already been demonstrated in order to obtain the marketing authorization. It could be argued that the patients were inadequately treated based on the fact that they continued to receive certain antihypertensive medication in the six week screening phase and their mean baseline blood pressure was 152/82mmHg. The target blood pressure in the study was less than 140/90mm which was higher than the target set by the British Hypertension Society.

In the Panel's view, given that 97% of patients in the study were diagnosed as hypertensives, that both the baseline blood pressure figure 150/82mmHg and the target figure in the study of less than 140/90mmHg were above the target for the population currently set by the British Hypertension Society (140/80mmHg), the study population could be considered as being a hypertensive population. The Panel did not consider that the report promoted Cozaar to delay the progression of diabetic nephropathy, reduce proteinuria in type 2 diabetes or heart failure *per se*. The outcomes were presented in the context of treating hypertension. No breach of Clause 3.2 of the Code was ruled in this regard. This ruling was appealed.

The Panel ruled no breach of Clause 3.2 with regard to the allegation that delivering the report to health professionals who had not attended the meeting in effect promoted Cozaar outside the marketing authorization. This ruling was appealed.

2 Reflection of the entire scientific session

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo stated that the meeting report did not represent a balanced, fair and objective evaluation of all the evidence. The meeting had three other oral presentations using AII antagonists to treat patients with type 2 diabetes and renal disease, two of which were in the same scientific session. Only a brief mention was given to one of these studies.

The complainants were unsatisfied with Merck Sharp & Dohme's view that this was a meeting report of the RENAAL study results. By definition, a meeting report should summarise, at the very least, a part of the meeting such as a scientific session. A breach of Clause 7.2 was alleged.

RESPONSE

Merck Sharp & Dohme stated that the report was clearly described as 'A report from …' and was headed 'RENAAL: A-II Antagonism with losartan is a new standard for treatment of hypertensive patients with Type 2 diabetes and nephropathy'. It in no way represented itself as an all-embracing conference report or a comprehensive review of any individual session. It quite clearly presented the headline data from RENAAL, in a publication produced by Merck Sharp & Dohme with Cozaar prescribing information on the back. It was neither biased nor unrepresentative in the presentation of the RENAAL results.

PANEL RULING

The Panel considered that the report was very clear about what it covered ie the results of the RENAAL study. Readers would not expect it to be a report of the whole meeting nor of the whole scientific session. The Panel did not consider there was a breach of Clause 7.2 of the Code as alleged and ruled accordingly. This ruling was not appealed.

3 Alleged disguised promotion

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo alleged that the meeting report was disguised promotion in breach of Clause 10.1 of the Code.

RESPONSE

Merck Sharp & Dohme stated that as indicated above the report included its logo, address and Cozaar prescribing information, clearly indicating the nature of the report; it was not disguised promotion.

PANEL RULING

The Panel did not consider that readers would be misled into thinking that the report was anything other than promotional material. It was provided by representatives and prescribing information was included. The Panel ruled no breach of Clause 10.1 of the Code. This ruling was not appealed.

4 Alleged failure to declare that the meeting was sponsored

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo stated that as the report was company sponsored, it was fully subject to the requirements of the Code. Due to

the alleged breaches detailed above, the report was also alleged to be in breach of the supplementary information to Clause 19.3.

RESPONSE

Merck Sharp & Dohme stated that it could not be in breach of the supplementary information to the Code. This related to a clear declaration of involvement in the production/distribution of conference reports etc. As indicated above, Merck Sharp & Dohme's involvement in this item was clear for all to see.

PANEL RULING

The Panel noted that the supplementary information, which gave guidance about the requirements of the Code, could not be breached. The supplementary information referred to by the complainants merely warned about the sponsorship of meeting reports and the need for them to comply with the Code. Clause 19.3 referred to meetings sponsored by companies and the need to disclose this in all of the papers relating to the meeting. The American Society of Hypertension meeting had not been sponsored by Merck Sharp & Dohme. The Panel therefore ruled no breach of Clause 19.3 of the Code. This ruling was not appealed.

B Exhibition panel, leavepiece and representative activities

The exhibition panel (ref 09-02 CZR.01.GB.10351.P6c.Q0.0901) was headed 'Results. Proven renal protection' followed by 'Helping you protect your hypertensive type II diabetic patients from dialysis and transplantation'. The claims were referenced to the RENAAL study. The results of the study were given.

The six page leavepiece (ref 09-02 CZR.01.GB.10361.B.2m.CW.0901) was headed 'Announcing landmark trial results'. One page referred to the demonstrated renal protection in the RENAAL study referring to '… landmark results in hypertensive type II diabetics'.

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo were concerned about information received from physicians that the exhibition panels and leavepieces in question bearing the renal and mortality endpoint results of the RENAAL study were being used by Merck Sharp & Dohme representatives at company sponsored meetings.

As previously stated the RENAAL study was designed to evaluate the effects of losartan on renal endpoints and mortality independent of blood pressure reduction by aiming to achieve similar blood pressure reductions in both the active and comparator arms. Hence, the study was not evaluating the effects of blood pressure reduction and as such the exhibition panel and leavepiece promoted Cozaar outside its licensed indication.

The existence of the leavepiece also demonstrated that Merck Sharp & Dohme was encouraging representatives to proactively discuss the RENAAL study results. Both of these activities were a breach of Clause 3.2.

Upon request, Merck Sharp & Dohme had not provided documentary evidence that it had forbidden representatives to proactively discuss the renal outcomes from the RENAAL study since Merck Sharp & Dohme considered it was promoting within the Cozaar marketing authorization.

Bristol-Myers Squibb and Sanofi-Synthelabo also expressed concerns about reports from physicians that reprints of the RENAAL article from the New England Journal of Medicine were being distributed unsolicited by Merck Sharp & Dohme representatives from stands at these meetings. A breach of Clause 3.2 was alleged and if the article was distributed without prescribing information there also would be a breach of Clause 11.1.

Once again, no documentary evidence was provided by Merck Sharp & Dohme that this activity was forbidden.

RESPONSE

Merck Sharp & Dohme stated that the complainants' assertion that RENAAL was designed to assess the effects of losartan on various endpoints, independent of its blood pressure lowering actions was incorrect. The study addressed the question of whether controlling blood pressure with losartan (an RAAS blocking drug) was better than controlling blood pressure with a non-RAAS regimen. The control of blood pressure was critical to this study. It was certainly true that the results shed light on the benefits of lowering blood pressure with losartan which did not appear to be associated with other blood pressure lowering agents, but to suggest that RENAAL was addressing an issue unrelated to blood pressure was untrue.

Merck Sharp & Dohme stated that it clearly had a fundamental differing of opinion with Bristol-Myers Squibb and Sanofi-Synthelabo, regarding whether RENAAL related to blood pressure. Merck Sharp & Dohme denied that the representatives were engaging in discussion of this study to promote Cozaar outside its licence. They were certainly making prescribers aware of the new evidence when losartan was used to lower blood pressure in a cohort such as was included in RENAAL. All promotional material included appropriate prescribing information, the representatives carried SPCs and, now that the full RENAAL results had been published, the representatives had reprints available to issue if requested.

PANEL RULING

The Panel noted its comments about the RENAAL study in point A1 above.

The Panel noted that both the exhibition panel and the leavepiece clearly referred to hypertensive type 2 diabetic patients. Cozaar was licensed for treatment of hypertension and this could include hypertensive type 2 diabetics. Neither the exhibition panel nor the

leavepiece mentioned that the patients in the study also had nephropathy. The materials referred to a risk reduction of 28% based on the differences at 4 years between a placebo group of 42 patients and the losartan group of 69 patients. The results showed a clear statistically significant difference between losartan and placebo.

The Panel noted that Merck Sharp & Dohme had been extremely careful in describing the study population as hypertensives with type 2 diabetes. The Panel considered that it was extremely likely that all the patients would be considered hypertensive by today's standards but this had not been demonstrated.

On balance the Panel considered that the exhibition panel and the leavepiece were not inconsistent with the Cozaar SPC. The product was clearly being promoted for the treatment of hypertension. The renal outcomes were presented as benefits to using losartan for blood pressure control. The Panel therefore ruled no breach of Clause 3.2 of the Code. This ruling was appealed.

With regard to the allegation that reprints of the RENAAL Study had been distributed unsolicited by Merck Sharp & Dohme, the Panel noted that Merck Sharp & Dohme stated that the reprint was distributed on request. There was an implication that representatives had been using the published paper.

The Panel considered that Merck Sharp & Dohme was using the published study for a promotional purpose. Such use had to comply with the Code. The Panel noted that Merck Sharp & Dohme's materials clearly set the results in the context of treating hypertension. It could be argued that the published paper was not quite so clear in that regard, however, on balance the Panel did not consider that use of the published paper meant that Merck Sharp & Dohme was promoting outside the licensed indications as alleged. The Panel therefore ruled no breach of Clause 3.2 of the Code in this regard. This ruling was appealed.

The Panel did not consider that the report had been provided unsolicited, making it available on the company stand was in effect soliciting such requests. Representatives had been providing it on request. It had been used as a reference in promotional material. Clause 11.1 referred to unsolicited use. The Panel therefore ruled no breach of Clause 11.1 of the Code. This ruling was not appealed.

C Leavepiece

The four page leavepiece (ref 09-02 CZR.01.GB.10341.B.20m.HO.0901) referred to RENAAL and when folded out to two pages the leavepiece stated that 'RENAAL proves COZAAR can help protect the kidneys of your hypertensive type II diabetic patients'. Details of the outcome of the study were given including the claim 'Clinical benefits of COZAAR in RENAAL were due to effects beyond blood pressure lowering'.

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo stated that the leavepiece provided further evidence that Merck Sharp & Dohme was using representatives to promote Cozaar for a use outside the marketing authorization. The leavepiece stated 'Helping you protect your hypertensive type II diabetic patients from dialysis and transplantation', 'RENAAL proves COZAAR can help protect the kidneys of your hypertensive type II diabetic patients' and 'The first time any antihypertensive has been shown in hypertensive type II diabetics to significantly reduce the need for dialysis and transplantation'.

This item would be used by representatives proactively and a breach of Clause 3.2 was alleged.

RESPONSE

Merck Sharp & Dohme stated that in the RENAAL study, the need for dialysis and transplantation was significantly reduced from 25.5% to 19.6%, p=0.002. To Merck Sharp & Dohme's knowledge, this was the first time that a medicine had significantly reduced this clinically important endpoint. (The closest corresponding figures from the Bristol-Myers Squibb and Sanofi-Synthelabo IDNT trial was 17.8% vs 14.2% p=0.07.) The message was clearly true – lowering the blood pressure of hypertensive diabetic patients with proteinuria using losartan, titrating the dose to 100mg if blood pressure was not controlled on 50mg and adding other antihypertensive medications if needed reduced the risk of requiring dialysis or a transplant.

PANEL RULING

The Panel noted its rulings in point A1 and B above. The leavepiece now at issue clearly referred to hypertensive type 2 diabetic patients. The Panel considered that on balance the leavepiece was not inconsistent with the Cozaar SPC. The product was clearly being promoted for the treatment of hypertension. The renal outcomes were presented as benefits to using losartan for blood pressure control. The Panel therefore ruled no breach of Clause 3.2 of the Code. This ruling was appealed.

D Alleged breach of Clause 2

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo alleged that by actively promoting Cozaar for an unlicensed indication, Merck Sharp & Dohme's activities could reduce confidence in and bring discredit upon the industry. A breach of Clause 2 was alleged.

RESPONSE

Merck Sharp & Dohme believed there was no case to answer with regard to the alleged breach of Clause 2 of the Code.

PANEL RULING

The Panel noted its rulings of no breach above. It did not consider that there had been a breach of Clause 2 of the Code which was used as a sign of particular censure and reserved for such circumstances. The Panel therefore ruled no breach of Clause 2 of the Code. This ruling was not appealed.

APPEAL BY BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHELABO

Bristol-Myers Squibb and Sanofi-Synthelabo stated that they appealed the rulings of no breach of Clause 3.2 of the Code at points A1, B and C.

The companies stated that Clause 3.2 required that the promotion of a medicine must not be inconsistent with the particulars listed in its SPC. The SPC for Cozaar stated that it was indicated for the treatment of hypertension.

Following the announcement of the RENAAL trial results at the American Society of Hypertension meeting in 2001 Merck Sharp & Dohme had actively referred to these results in its promotion of Cozaar.

The primary endpoints in the RENAAL trial were measures of nephrological morbidity and of mortality, not blood pressure. Although blood pressure reduction was required in the trial, RENAAL was not a study of target blood pressure attainment. The RENAAL trial was designed such that equivalent blood pressure control would be achieved in both the placebo- and losartan-based treatments arms, thereby allowing testing of the hypothesis that, in an equivalent population, a particular agent might confer benefits beyond blood pressure lowering alone. Subject to assessment by the relevant licensing authorities, the results of the RENAAL study might be expected to result in a licensed indication for Cozaar, additional to the current indication for the treatment of hypertension alone.

Although hypertension often coexisted with diabetic nephropathy, these two conditions represented different pathologies with likely distinct underlying mechanisms. The safety and efficacy of Cozaar in the treatment of diabetic renal disease had not been assessed by the relevant regulatory authorities and Cozaar was currently indicated only for the reduction of blood pressure.

The companies maintained that by including such claims as 'Clinical benefits of Cozaar in RENAAL were due to effects beyond blood pressure lowering' and 'Proven renal protection' in its promotional materials, Merck Sharp & Dohme ascribed properties to Cozaar which went beyond the benefits expected from the treatment of hypertension alone.

The companies therefore believed their complaint that Merck Sharp & Dohme was in breach of Clause 3.2 should be upheld.

COMMENTS FROM MERCK SHARP & DOHME

Merck Sharp & Dohme stated that the main concern was that promotion of the RENAAL results was outside the current licence. Cozaar was currently approved 'for the treatment of hypertension'. By implication therefore, any patient in whom blood pressure (BP) was judged too high and in whom BP reduction was considered appropriate was within the current licence. This would include many diabetic patients, and almost all diabetic patients with nephropathy.

The whole point of treating hypertension was to reduce the incidence of hypertension-related events such as stroke, myocardial infarction and renal failure. In most cases, there was no accurate estimate of the extent to which these endpoints were reduced by medicines because the studies had not been done. One had to make do with a combination of beneficial effects on surrogate markers such as the BP level itself, reduction in proteinuria (as a marker of renal involvement) and reduction of left ventricular (LV) mass (as a marker of cardiac involvement). The only difference now was that there was an accurate estimate of the beneficial effects of losartan in reducing renal failure in this portion of hypertensive patients.

Merck Sharp & Dohme stated that Bristol-Myers Squibb and Sanofi-Synthelabo clearly considered it acceptable to link BP reduction with improvements of the surrogates; why not with the clinical endpoint too, when the data existed? For example, it seemed acceptable for them to say 'When lowering BP with Aprovel in diabetic hypertensive patients with proteinuria, proteinuria is reduced', implying a renal benefit and 'When lowering BP with Aprovel in hypertensive patients with LV hypertrophy, LV mass is reduced', implying a cardiac benefit . The companies seemed to consider it acceptable to go on to say Aprovel was therefore 'an effective agent in the treatment of Left Ventricular Hypertrophy' and further down the page, references to Aprovel being 'an effective agent in the treatment of heart failure'. Aprovel was only licensed for the treatment of essential hypertension.

Addressing the specific points raised in the appeal.

RENAAL was not a study of target BP attainment
RENAAL was very much a study of 'target blood pressure attainment' – treatment was continually increased in an attempt to reach target.

Hypertension and diabetic nephropathy have different underlying pathologies To say that the underlying mechanisms of hypertension and nephropathy were distinct from each other was untrue. Hypertension led to renal disease, and renal disease led to hypertension – any undergraduate medical textbook would illustrate this. To suggest that hypertension and diabetic nephropathy simply 'co-existed', as if by chance, was also untrue. As discussed above, not all hypertensives had diabetic nephropathy, but the converse was not true. All patients with diabetic nephropathy, judged by proteinuria and renal dysfunction, should be considered for antihypertensive therapy.

Promotional claims 'Effects beyond BP lowering' – The results of RENAAL added to our understanding that how you lower blood pressure might be more than simply hitting BP targets. In this sense, the results of RENAAL were beyond a simple concept of BP control alone, there being clinically important differences despite equivalent BP reduction. Perhaps the claim should have read '… beyond BP lowering alone'. Nonetheless, the claim did not amount to promotion outside the licence, since lowering BP was the reason for the prescription. Merck Sharp & Dohme was not encouraging the average UK GP to prescribe Cozaar because a patient had diabetes or proteinuria, but because they had to hit the NICE guidelines target of a BP of below 135/85 in these patients.

'Proven renal protection' Merck Sharp & Dohme believed this was exactly what RENAAL had shown.

Throughout the RENAAL promotion, Merck Sharp & Dohme's message had been clearly linked to hypertension – patients with diabetes and this degree of nephropathy (proteinuria and increasing creatinine) were, for all practical purposes, hypertensive and in need of BP reduction. Cozaar reduced the BP of these patients and this resulted in a reduction in the need for dialysis and transplantation. Merck Sharp & Dohme believed that there had been no breach of Clause 3.2.

FURTHER COMMENTS FROM BRISTOL-MYERS SQUIBB AND SANOFI-SYNTHELABO

Bristol-Myers Squibb and Sanofi-Synthelabo noted Merck Sharp & Dohme's comments on specific points raised in the appeal but maintained their position.

The companies objected to Merck Sharp & Dohme's reference to their own Aprovel material as this was not the subject of the complaint and was irrelevant to the appeal.

APPEAL BOARD RULING

The Appeal Board noted Merck Sharp & Dohme's reference to Aprovel material that had been issued by Bristol-Myers Squibb and Sanofi-Synthelabo to develop Merck Sharp & Dohme's argument. The appeal related to Merck Sharp & Dohme's material and would be considered on its own merits. The Appeal Board made no comment on the acceptability or otherwise of the Aprovel material. Merck Sharp & Dohme could submit a complaint about the Aprovel material if it so wished.

The Appeal Board considered that there was a difference between promoting a product for a licensed indication and promoting the benefits of treating a condition.

Although the RENAAL study was not a study about the treatment of hypertension *per se* it was a study in patients in whom the lowering of blood pressure would be considered beneficial. The study was in patients diagnosed as type 2 diabetics with nephropathy. The majority of patients recruited into the study, although already receiving antihypertensive therapy, were nonetheless still considered to be hypertensive, that is they were sub-optimally controlled. During a run-in period all ACE inhibitors or AII antagonists were discontinued and replaced with other classes of antihypertensive agent. Patients were then randomised to receive either losartan or placebo in addition to their existing medication. The Appeal Board noted that the design of the study was such that both hypertensive and normotensive patients with type 2 diabetes and neuropathy were eligible. In reality 93.5% of the patients were already receiving antihypertensive therapy and an additional 3% of the patients were hypertensive although they were not receiving antihypertensive therapy. The Appeal Board noted Merck Sharp & Dohme's submission that the 3% of patients who were not considered hypertensive at the time the study started would be by today's standards. The study was designed to evaluate the renoprotective effects of losartan. The study report ended with the statement 'In summary, losartan led to significant improvement in renal outcomes that was beyond that attributable to blood-pressure control in patients with type 2 diabetes and nephropathy'.

The Appeal Board was concerned that the promotional material at issue used claims such as 'Proven renal protection', 'Clinical benefits of Cozaar in RENAAL were due to effects beyond blood pressure lowering' and 'results that demonstrate renal protection'. The Appeal Board noted that Cozaar was not licensed for renal protection; its only licensed indication was to lower blood pressure. In the Appeal Board's view the renoprotective effects had been given undue emphasis and had not been placed sufficiently within the context of treating hypertension such that the material appeared to promote Cozaar for its renoprotective effect.

A Report from the American Society of Hypertension Meeting

The report had been used by Merck Sharp & Dohme's representatives and had been distributed to health professionals who had not attended the meeting. The Appeal Board noted its comments above and considered that the report promoted Cozaar beyond the terms of the marketing authorization and was inconsistent with the Cozaar SPC. Any use of the report was therefore inappropriate. Breaches of Clause 3.2 were ruled. The appeals with regard to the report were successful. The Appeal Board noted that the report was no longer in use as it had been superseded by the published report of the RENAAL study.

B Exhibition panel, leavepiece and representative activities

With regard to the exhibition panel and the six page leavepiece the Appeal Board noted its comments above. The exhibition panel was headed 'Results. Proven renal protection' and sub-headed 'Helping you protect your hypertensive type II diabetic patients from dialysis and transplantation'. Although the terms 'anti-hypertensive' and 'hypertensive type II diabetic' had been used within the body of the panel the Appeal Board's view was that it had not been made clear that the reason to prescribe Cozaar was for the treatment of hypertension. Similarly the relevant sections of the leavepiece emphasised the renal effects of Cozaar without making it clear that it must be prescribed to lower blood pressure. A breach of Clause 3.2 was ruled. The appeal with regard to the exhibition panel and the six page leavepiece was successful.

With regard to the representative's use of reprints of the published RENAAL paper, the Appeal Board noted Merck Sharp & Dohme's original response that these were handed out if requested. The Appeal Board considered that making the reprints available in response to a specific request (ie using the paper reactively not proactively) was acceptable and on this narrow basis ruled no breach of Clause 3.2. The appeal on this point was unsuccessful.

C Leavepiece

With regard to the four page leavepiece the Appeal Board noted its comments above and ruled a breach of Clause 3.2 of the Code. The appeal on this point was successful.

Complaint received **7 December 2001**

Case completed **24 April 2002**

CASE AUTH/1266/12/01

HEALTH AUTHORITY v ABBOTT LABORATORIES

Obesity symposium

A health authority complained about a meeting entitled 'Obesity – enough is enough' held by Abbott Laboratories in Cardiff. The registration form offered overnight accommodation for one to two persons and a banquet held at Cardiff Castle following the meeting. The complainant alleged that the documentation for the event appeared to breach the Code in that the banquet appeared to invite partners and overnight accommodation was offered.

The Panel noted Abbott's submission that no spouses or accompanying partners were invited to attend. This was not clear from the registration form in which the first box to be ticked was 'I wish to attend the meeting and the second two boxes were 'I require overnight accommodation for ONE PERSON' and 'I require overnight accommodation for TWO PERSONS'. The fifth box was 'I/We wish to attend the Banquet at Cardiff Castle on Saturday evening'. The Panel considered that the registration form implied that only the person completing the registration form would be attending the meeting but that they could invite someone else to accompany them to the banquet and to stay overnight. The Panel considered that the registration form was inadequate and it was inappropriate to describe the Saturday evening dinner as a 'banquet'. The Panel considered that Abbott had not maintained a high standard and ruled a breach of the Code.

The Panel was concerned that the dinner following the meeting was described as a banquet which gave the impression that the event would be lavish. In reality this was not so. The Panel considered that the costs of the meeting did not exceed the level that the recipients would adopt if paying for themselves and hence did not consider that the actual arrangements for the meeting were unacceptable. No breach of the Code was ruled.

The Panel did not consider that the circumstances warranted a ruling of Clause 2 which was used as a sign of particular censure and no breach of that clause was ruled.

On appeal by the complainant, the Appeal Board noted that in Abbott's submission to the Panel it had stated that four rooms were upgraded to double rooms to accommodate a spouse/partner 'who was also a health professional or qualified as an appropriate administrative staff'. In response to the appeal Abbott amended this to twenty-one double rooms. The response to the Panel had not provided sufficient detail about the delegates, whether they were GPs, nurses, dieticians, etc. The Appeal Board was extremely concerned about the discrepancy between Abbott's two submissions. It appeared that it was not until the complainant had appealed that Abbott had fully investigated the matter.

The Appeal Board considered that the educational content of the meeting and the hospitality for those attending the meeting were not unreasonable. The Appeal Board considered the wording on the invitation facilitated spouses/partners who did not qualify as proper delegates in their own right attending the meeting at the company's expense. In the Appeal Board's view the wording of the invitation suggested that inappropriate hospitality for spouses/partners was being offered. A breach of the Code was ruled.

The Appeal Board was concerned that as a result of the appeal it had become apparent that Abbott had supplied incorrect information to the Panel. It noted its ruling of a breach of the Code above and considered that Abbott's conduct was such as to as to bring discredit upon, or reduce confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

COMPLAINT

A health authority complained about a symposium organised by Abbott Laboratories Limited.

The meeting entitled 'Obesity – enough *is* enough' was held at a hotel in Cardiff on 1 December 2001. The meeting, chaired by a general practitioner, ran from 11.00 to 5.30pm. There were breaks for lunch and for coffee, totalling 1.5 hours. 4.5 hours of postgraduate education allowance had been granted. A registration form accompanied the invitation and was to be completed by attendees. Overnight accommodation was offered for one to two persons as was a banquet held at Cardiff Castle following the meeting.

The complainant alleged that the documentation for the event appeared to breach the Code in that the banquet appeared to invite partners and overnight accommodation was offered.

In writing to Abbott the Authority drew attention to Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

Abbott stated that the meeting was a one day scientific meeting. Those invited comprised local general practitioners, general practitioners known to have a specialist interest in the management of obesity and allied health professionals such as practice nurses. If requested by the GP, appropriate practice administrative staff such as practice managers, were also permitted to attend.

The invitation was not sent out as a general mailing. As part of their usual visit to a GP, representatives were briefed to personally invite the relevant health professional (or to extend the invitation to appropriate staff nominated by the GP), and to leave the agenda and invitation as requested. Representatives were specifically instructed to ensure that copies of the agenda and invitation were not left freely available in the practice building. All Abbott representatives were fully cognisant of the requirement of Clause 19.1 such that meetings and hospitality might not be extended beyond members of the health professions or appropriate administrative staff.

The registration form accompanying the agenda and invitation included reference to a requirement for accommodation for two persons. This statement was included so that any interest in the event made by other practice members, be they allied health professionals or appropriate administrative staff, could be appropriately documented.

Abbott submitted that in accordance with Clause 19.1 of the Code, details and documentation for the meeting were checked by authorised signatories prior to approval. On reflection, Abbott could see how the design of the registration form might have led to confusion, and future forms of this nature would be appropriately amended. However, the medical representatives were fully briefed to decline any requests for spouses not qualifying as health professionals or appropriate administrative staff to attend this event, in accordance with Clause 19.1. The invoice showed that spouses did attend the event. These were all either health professionals (three nurses) or appropriate practice administrative staff (one general practice manager), which was in accordance with Clause 19.1.

In total, approximately 200 invitations were left with health professionals and 72 acceptances were received. These comprised GPs and associated health professionals or administrative staff only, ie practice managers and practice nurses. No non-health professionals attended as delegates. Requests were verbally made by some attendees to bring spouses/partners to the evening event and this was declined by the medical representative.

The total number of day delegates, including Abbott staff and speakers, was 90. Including day delegate rates, lunch, soft drinks and equipment hire, the total cost for the day's event was £62 per head.

The hospitality offered by Abbott was extended to delegates only, and thus, no non-health professionals or inappropriate administrative staff received Abbott hospitality. Overnight accommodation was prioritised to those travelling furthest to the meeting. Some attendees were required to travel from Swansea and West Wales to attend the event. A total of 39 single rooms were booked for the evening. Four of these were requested to be upgraded to double rooms at the request of the attendee. This was because the accompanying person was a spouse or partner who was also a health professional or who qualified as an appropriate administrative staff. All delegates were told that they were responsible for all extra charges made to their rooms, apart from car parking.

Abbott stated that the evening event was held in the Crypt Restaurant in Cardiff Castle. A standard 3 course meal was offered, at a total cost of £29.50 per attendee, inclusive of alcoholic beverages. No other entertainment or hospitality was offered on the evening. In total, there were 61 attendees, all of whom were health professionals, Abbott staff, invited speakers or appropriate administrative staff.

In summary, Abbott believed that this event was conducted in accordance with the requirements of the Code and denied a breach of Clauses 2, 9.1 and 19.1.

PANEL RULING

The Panel noted that the supplementary information to Clause 19.1 of the Code permitted spouses and accompanying persons to be invited to events. Such persons must not attend the meeting unless they qualified as a proper delegate in their own right and must not receive any associated hospitality at the company's expense. The entire costs which their presence involved was the responsibility of those they accompanied. The supplementary information stated that administrative staff might be invited to meetings where appropriate.

The Panel noted Abbott's submission that no spouses or accompanying partners were invited to attend. This was not clear from the registration form which required the name of the person completing it. The first box to be ticked was 'I wish to attend the meeting on Saturday, 1 December. The second two boxes were 'I require overnight accommodation for ONE PERSON' and 'I require overnight accommodation for TWO PERSONS'. The fifth box was 'I/We wish to attend the Banquet at Cardiff Castle on Saturday evening'. The Panel considered that the registration form implied that only the person completing the registration form would be attending the meeting but that they could invite someone else to accompany them to the banquet and to stay the night. Spouses and partners could attend in accordance with the supplementary information to the Code but only if their costs were not paid by the company. The Panel did not accept Abbott's submission that the registration form could be used by more than one delegate to the scientific meeting. The registration form should have been designed differently. It was inadequate to state that the representatives delivering the invitations would decline requests to bring spouses. This was not what was stated on the registration form which should have clearly given full details about the arrangements.

The Panel was concerned that the dinner following the meeting was described as a banquet which gave the impression that the event would be lavish. In reality this was not so as the cost per head of £29.50 included three courses and drinks which the Panel considered was not unreasonable. The cost of the hotel accommodation was not unreasonable. The Panel considered that the costs of the meeting did not exceed the level that the recipients would adopt if paying for themselves.

The Panel did not consider that the actual arrangements for the meeting were unacceptable. No breach of Clause 19.1 of the Code was ruled.

The Panel considered that Abbott had not maintained a high standard. The registration form was inadequate as it failed to make the position clear with regard to spouses and other accompanying persons. Further it was inappropriate to describe the Saturday evening dinner as a 'banquet'. Although the arrangements were ruled not to be in breach of Clause 19.1, the paperwork was inadequate. The Panel therefore ruled a breach of Clause 9.1 of the Code.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use. No breach of Clause 2 was ruled.

The Panel queried whether the content of the meeting was appropriate for administrative staff such as the practice manager who attended. The agenda was aimed at the clinical effects of obesity and its treatment. There appeared to be little or nothing that was relevant to practice administration. There was no complaint in this regard. It appeared that if a GP requested that their practice manager attend this would be accepted by Abbott. The Panel considered that the company would be well advised to decide itself whether its meetings were relevant to administrative staff rather then allow such people to be invited in response to a request from the GPs invited.

APPEAL BY THE COMPLAINANT

The complainant stated that examination of Abbott's letter of response and the accompanying invoices led to further questions. In this regard the complainant noted that a particular name and room number appeared twice but was not declared on the car parking sheet as a relative attending. The rooms seemed to be divided between two different costs. If these equated to single and double rooms then there were far more partners attending than declared by the company. It was also apparent from the car parking sheet that some of the couples brought two cars. Given that the invoices also showed for the hire of a coach to transport delegates from the hotel to the dinner at the castle this implied that the partners did not attend the conference. Although initials were not given on the accommodation sheet it was clear that at least two and maybe more of the delegates that stayed at the hotel were general practitioners in the Cardiff area and lived in the Cardiff area.

The complainant requested confirmation that the complete set of invoices were included and that Abbott could confirm that it provided no alcoholic beverages at any time to the delegates.

The complainant wished it to be reconsidered whether the hospitality was really secondary to the purpose of the meeting. Would general practitioners attending postgraduate events organised by continuing professional development departments travel from West Wales to an event of this kind in Cardiff unless there was some other motivation? For example there was a very active and well run postgraduate department in the Swansea area that provided this type of conference on a regular basis. Would general practitioners from the Cardiff area attending a postgraduate event at a local postgraduate centre book into a local hotel for the night, take a dinner at the Castle, hire transport to take them back to the hotel and stay for breakfast?

The complainant stated that he was aware of the culture that had developed, in South Wales at least, of general practitioners expecting a level of hospitality from pharmaceutical companies that he believed the general public would not expect or understand. He realised the difficulties that this presented to local pharmaceutical representatives. However, he believed the continuation of the practice of organising such a meeting where the main attraction was an overnight stay in a first class Cardiff hotel with a dinner in Cardiff Castle rather than the scientific matter did bring the industry into disrepute.

COMMENTS FROM ABBOTT

Abbott noted that the complainant asked a number of questions based on his scrutiny of the requisite invoices as supplied by Abbott. He also requested a statement from Abbott that the complete set of invoices were included. Abbott noted that a complete set of invoices were forwarded to the complainant by the Authority.

In the complainant's correspondence he asked a number of questions relating to the invoice from the hotel. Abbott responded to these in the order used by the complainant.

The name which appeared twice belonged to a dietician and a member of the National Obesity Forum (NOF) who attended the meeting as a delegate and stayed the night before the meeting in order to provide assistance to some of the speakers who were also members of the NOF. The relevance of the reference to car-parking was not clear.

The rooms were divided into two different costs, £105, representing single occupancy and £130, representing double occupancy. A number of delegates (either health professionals or relevant administrative staff with an interest in obesity) invited to the meeting were also spouses, partners or colleagues who shared accommodation for their own convenience and/or as a means of keeping costs down. Previous correspondence relating to this matter informed the complainant that four spouses or partners attended as delegates in their own right. This was based on scrutiny of the number of spouses/partners detailed by name on the hotel invoice. The observation by the complainant that there was a greater number of double rooms than Abbott originally assumed was correct, and it had obtained full details on these. In summary, of the 21 double rooms, 8 were each occupied by 2

doctors, 10 were each occupied by a doctor and an allied health professional, 1 was occupied by an Abbott employee and 2 rooms were each occupied by 2 dieticians. All of these guests were delegates at the meeting. Abbott would like to apologise unreservedly for any confusion this might have caused but it would also like to reiterate that attendance at the conference, and accommodation at the hotel, was strictly limited to either health professionals or relevant administrative staff with an interest in obesity. All Abbott representatives were fully cognisant of the requirement of Clause 19.1 such that meetings and hospitality might not be extended beyond members of the health professions or appropriate administrative staff.

With regard to the complainant's comment that some of the couples brought two cars, this might well be true but Abbott stated that its comments with regards to accommodation were equally applicable to the provision of car-parking.

With regard to the complainant's comment that the hire of a coach to transport delegates from the hotel to the dinner at the castle implied that the partners did not attend the conference, Abbott stated that the nature of the question was unclear. Transport was provided from the hotel to Cardiff Castle and back for all delegates. To reiterate, all delegates that attended the conference or the evening meal were either health professionals or relevant administrative staff with an interest in obesity.

With regard to the complainant's comment that at least two of the delegates were GPs in the Cardiff area, Abbott stated that the purpose of this scientific meeting was to provide education and a chance to meet key-opinion leaders to physicians with an interest in obesity from all over Wales. As many of the delegates had travelled considerable distances, accommodation was offered, with priority given to those delegates who had the furthest distance to travel. Most local delegates did not request accommodation. Only two rooms were provided for delegates who worked in Cardiff. In these cases, specific individual circumstances resulted in their request for accommodation.

Abbott stated it was quite clear from the invoice that no alcoholic beverages were provided as part of the scientific meeting. As part of the evening meal some alcoholic beverages were provided but only as part of the inclusive price of the three-course meal.

Abbott submitted that the arrangements were in accordance with Clause 19.1 of the Code. From the outset, it was made clear that this meeting was educational, as confirmed by the post graduate education allowance approval. Hospitality was secondary to the purpose of the meeting and only provided to health professionals or appropriate administrative staff. The level of hospitality was appropriate and not out of proportion to the occasion and the costs involved did not exceed the level which the recipients would normally adopt when paying for themselves. The appellant offered only a personal opinion that remained at odds with the evidence of the case and with the Panel's ruling.

Abbot also denied a breach of Clause 2. The company was firmly of the opinion that its staff were aware of the requirements of the Code and made every effort to abide by the Code at all times.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant was not able to comment on Abbott's response to the appeal. Another member of staff at the health authority stood in for the complainant and made no comment on Abbott's response.

APPEAL BOARD RULING

The Appeal Board noted that there was a discrepancy between Abbott's response to the complaint and its response to the appeal with regard to the number of double rooms. In its submission to the Panel, Abbott had stated that four rooms were upgraded to double rooms to accommodate a spouse/partner 'who was also a health professional or qualified as an appropriate administrative staff'. In response to the appeal Abbott amended this to twenty-one double rooms. The response to the Panel had not provided sufficient detail about the delegates, whether they were GPs, nurses, dieticians, etc. The Appeal Board was extremely concerned about the discrepancy between Abbott's two submissions. It appeared that it was not until the complainant had appealed that Abbott had fully investigated the matter.

The Appeal Board expressed surprise about the high number of double rooms which had been booked and queried whether all accompanying spouses/partners qualified as delegates at the meeting in their own right. There was no allegation in this regard.

The Appeal Board noted that the Panel had ruled a breach of Clause 9.1 in relation to the failure of the registration form to make the position clear with regard to spouses and other accompanying persons and the description of the dinner as a banquet. The Appeal Board considered that the educational content of the meeting and the hospitality for those attending the meeting were not unreasonable. It noted that the invited audience were from all over Wales. It was not unreasonable to provide overnight accommodation in such circumstances. The Appeal Board considered the wording on the invitation facilitated spouses/partners who did not qualify as proper delegates in their own right attending the meeting at the company's expense. The Appeal Board noted the supplementary information to Clause 19.1 which stated, *inter alia*, that the impression created by the arrangements for any meeting must be kept in mind. In the Appeal Board's view the wording of the invitation suggested that inappropriate hospitality for spouses/partners was being offered. A breach of Clause 19.1 was ruled. The appeal on this point was successful.

The Appeal Board was concerned that as a result of the appeal it had become apparent that Abbott had supplied incorrect information to the Panel. It noted its ruling of a breach of Clause 19.1 above and considered that Abbott's conduct was such as to as to bring discredit upon, or reduce confidence in the pharmaceutical industry. A breach of Clause 2 was ruled. The appeal on this point was successful.

Complaint received **17 December 2001**

Case completed **13 June 2002**

CASE AUTH/1272/1/02

PHARMACIA v GLAXOSMITHKLINE CONSUMER HEALTHCARE

Promotion of NiQuitin CQ lozenge

Pharmacia complained about an advertisement for NiQuitin CQ Lozenges (nicotine polacrilex) 2mg and 4mg issued by GlaxoSmithKline Consumer Healthcare which featured the heading 'Cigarette End'. NiQuitin CQ was a form of nicotine replacement therapy (NRT) for relief of nicotine withdrawal symptoms, including craving associated with smoking cessation.

The claim 'The NiQuitin CQ 4mg Lozenge has a success rate unsurpassed by any other form of NRT,…' appeared in a section headed 'Unsurpassed NRT efficacy' and a footnote read 'Six month continuous abstinence rates for 4mg Lozenge compared with pooled odds ratios (ORs) for other NRT forms from Cochrane Group meta-analysis'. Pharmacia noted that in deriving this claim GlaxoSmithKline Consumer Healthcare had compared the results of its single study (data on file) [subsequently submitted for publication as Schiffman *et al*] with the Cochrane meta-analysis which contained 100 trials of NRT. Pharmacia challenged the validity of this comparison; to establish a claim of top parity there should be evidence from controlled head-to-head studies showing no evidence of difference. The OR for the NiQuitin CQ 4mg lozenge at 6 months was 2.76 and at 12 months 2.69, (data on file). Individual studies within the Cochrane database included the following 12 month data: nicotine gum, OR 3.23 (Herrera *et al* 1995); nicotine patch, OR 2.93 (Sachs *et al* 1993); nicotine nasal spray, OR 2.92 (Sutherland *et al* 1992). Pharmacia considered that as these studies individually showed higher ORs, to suggest top parity was misleading.

The Panel noted that Schiffman *et al* examined the safety and efficacy of NiQuitin 2mg and 4mg in 1818 patients for smoking cessation; the odds of being abstinent after six weeks of treatment were 2.1 to 3.7 times greater among those on active lozenge (2mg and 4mg) than those on placebo. The authors stated that 'both the absolute success rates and the ORs achieved by the nicotine lozenge were in the upper range of those observed in previous studies of other forms of NRT, suggesting that this may be a particularly effective NRT treatment'. The authors also noted that 'definitive conclusions about comparative efficacy would require a randomized head-to-head comparison'.

The Cochrane meta-analysis of 108 trials in 35,600 smokers gave ORs for each form of NRT which met the search criteria.

The Panel considered that the claim created the impression that the NiQuitin CQ lozenge had been directly compared with all other forms of NRT therapy and that was not so. The heading to the claim 'Unsurpassed NRT efficacy' compounded the impression given. The Panel also noted Schiffman *et al*'s comments about the need for direct comparative studies in this regard. The Panel considered that the footnote did not negate the impression given; it was an established principle under the Code that an otherwise misleading claim could not be qualified by a footnote. The Panel considered the claim misleading as alleged. Breaches of the Code were ruled.

Schiffman *et al* showed that placebo treatment compared with active lozenge resulted in a significantly greater 28 day continuous abstinence at 6 weeks both for 2mg lozenge (OR=2.10) and the 4mg lozenge (OR=3.69). The Cochrane meta-analysis included individual studies with other forms of NRT in which the OR was greater than the OR for NiQuitin Lozenge; ORs for each were provided ranging from 1.66 to 2.27. The Panel considered that this was a difficult area and noted its general comments above regarding Schiffman *et al* and the authors' conclusions.

The Panel considered that given its ruling that the claim was misleading, the data which did not include a direct comparison did not substantiate the claim at issue and breaches of the Code were ruled.

Pharmacia referred to a number of claims all of which were referenced to data on file [Schiffman *et al*]. The claim '… with more dependent smokers tripling their chances of successfully quitting with the NiQuitin CQ 4mg Lozenge compared with placebo at 6 months' appeared as the second half of the same sentence as the claim at issue above. Pharmacia was concerned that the efficacy of NiQuitin CQ 4mg Lozenge was exaggerated. The data on file showed that the 6 month continuous abstinence rates were: 23.6% (active) vs 10.2% (placebo), 2.31 times greater than placebo and did not substantiate the 'tripling' claim of efficacy. GlaxoSmithKline Consumer Healthcare had substantiated the claim by using ORs. Pharmacia considered that this did not accurately represent the relative number of individuals actually quitting smoking in the clinical trial, as health professionals would expect, and the more appropriate end-point was the relative risk (RR). This reflected the actual number of individuals who successfully quit smoking in the active versus placebo group.

The Panel noted that although the claim at issue gave the impression that a dependent smoker would be three times more likely to have successfully quit smoking with NiQuitin CQ 4mg Lozenges than with placebo at 6 months some readers might assume that it meant that 3 times as many smokers would quit on NiQuitin CQ than on placebo. This was not so. The Panel considered the claim misleading as the basis of the calculation had not been made sufficiently clear. Breaches of the Code were ruled. Given the data the Panel did not consider the claim exaggerated as alleged. No breach of the Code was ruled on this point.

The claim '… the NiQuitin CQ 2mg Lozenge can more than triple a smoker's chance of quitting compared with placebo' appeared in the section headed 'The importance of compliance'. A footnote read 'OR measured at 6 weeks, users taking more than the median dose (8.2 4mg Lozenges, 6.7 2mg Lozenges per day) during the first two weeks of

treatment'. Pharmacia was concerned that the efficacy of NiQuitin CQ 2mg Lozenge was also exaggerated as the 'Data on file' quoted abstinence rates: 57.7% (active) vs 29.9% (placebo); this was 1.92 times greater than placebo which did not substantiate the 'triple' claim.

The Panel considered that some of its comments above were relevant here. The Panel considered that the claim was misleading as the basis of the calculation had not been made sufficiently clear. The Panel noted that it was an established principle that an otherwise misleading claim could not be qualified by a footnote. The claim was misleading as alleged and a breach of the Code was ruled. The Panel did not consider the claim exaggerated as alleged; no breach of the Code was ruled on this point.

The claim '… smokers who take above the median dose of 8.2 NiQuitin 4mg Lozenges per day can increase their chances of success by over five times compared to placebo' also appeared in the compliance section. A footnote read 'OR measured at 6 weeks, users taking more than the median dose (8.2 4mg Lozenges, 6.7 2mg Lozenges per day) during the first two weeks of treatment'. Pharmacia was concerned again that the efficacy of NiQuitin CQ 4mg Lozenge was exaggerated as the actual figures for abstinence were 56.8% (active) vs 19.2% (placebo) which equated to 2.96 times greater than placebo. This also did not substantiate the efficacy claim.

The Panel considered that its ruling above was relevant here; a breach of the Code was ruled as alleged. The Panel did not consider the claim exaggerated as alleged; no breach of the Code was ruled on this point.

Pharmacia Limited complained about an advertisement for NiQuitin CQ Lozenges (nicotine polacrilex) 2mg and 4mg (ref NCQ/PWT/1101/001) issued by GlaxoSmithKline Consumer Healthcare which featured the heading 'Cigarette End' and discussed NiQuitin CQ Lozenges in relation to quitting, efficacy, compliance, dose determination, method of dose, dosage schedule and a stop smoking plan. NiQuitin CQ was a form of nicotine replacement therapy (NRT) for relief of nicotine withdrawal symptoms, including craving associated with smoking cessation.

1 Claim 'The NiQuitin CQ 4mg Lozenge has a success rate unsurpassed by any other form of NRT,…'

This claim appeared in a section headed 'Unsurpassed NRT efficacy' and was referenced to Data on file, 2000 and Silagy *et al* 2001 (Cochrane meta-analysis). An obelus referred the reader to a footnote which read 'Six month continuous abstinence rates for 4mg Lozenge compared with pooled odds ratios (ORs) for other NRT forms from Cochrane Group meta-analysis'.

COMPLAINT

Pharmacia noted that this claim was referenced to GlaxoSmithKline's 'Data on File' and compared to the Cochrane meta-analysis; GlaxoSmithKline Consumer Healthcare was thus comparing the results of its single study with a meta-analysis which contained 100 trials of NRT. It was not valid to make a comparison of a single study to a pooled analysis of data. Indirect comparisons of this type could be extremely misleading. To establish a claim of top parity there should be, at the very minimum, evidence from controlled head-to-head studies showing no evidence of difference. There were no trials of this kind and GlaxoSmithKline Consumer Healthcare had used an indirect comparison to make this claim. Pharmacia alleged a breach of Clauses 7.2 and 7.3 of the Code.

GlaxoSmithKline Consumer Healthcare had used odds ratios (ORs) in making its efficacy claims ie the higher the OR the greater the efficacy. The OR for the NiQuitin CQ 4mg lozenge at 6 months was 2.76 and at 12 months 2.69 (Data on file). Using this method of comparing ORs there were individual studies within the Cochrane database with other forms of NRT which demonstrated better ORs over a 6-12 month time scale. These for example included the following 12 month data: nicotine gum, OR 3.23 (Herrera *et al* 1995); nicotine patch, OR 2.93 (Sachs *et al* 1993); nicotine nasal spray, OR 2.92 (Sutherland *et al* 1992). These studies individually showed higher ORs and to suggest top parity was misleading and potentially invalidated the unsurpassed claim. Pharmacia alleged a breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated that this was a top parity claim, and the complainant suggested that one should not rely on a single study to compare with a large number of studies as reported in the Cochrane meta-analysis.

GlaxoSmithKline Consumer Healthcare submitted a table based on The Cochrane Review (Silagy *et al*) which gave ORs for the different NRT formats and stated that these ORs were largely independent of the duration of therapy.

GlaxoSmithKline Consumer Healthcare stated that the allegations were incorrect and that the comparison it had made was legitimate. The underlying purpose and objective of meta-analysis (as conducted by the Cochrane Tobacco Addiction Review Group and others) was to review and synthesise all of the available qualifying evidence from randomized controlled trials so as to assist healthcare decision makers reach informed and evidence based decisions; indeed, the very purpose of meta-analysis, which had become the premiere way of assembling and evaluating medical evidence, was precisely to draw conclusions from data from numerous trials conducted over a 20 year period using different protocols, populations, advice and support. Because the OR was robust in the face of variation in procedures, support etc (as discussed below), it was used for such systematic reviews by the prestigious Cochrane Tobacco Addiction Review Group amongst others. This sort of pooling, in contrast to 'cherry-picking' of studies to suit a purpose, was considered an important method of drawing conclusions from the scientific literature.

Such systematic review and comparisons based on all available evidence was useful and important regardless of the number of studies involved. In an area where only one study was available, that evidence was extremely useful. Indeed, it noted that the Cochrane collaboration in numerous instances tabulated results from single studies where they constituted the extant body of evidence.

It was important to note that a manuscript from the study which comprised the data on file had been subjected to scientific peer review and accepted for publication in Archives of Internal Medicine (Schiffman *et al*). To attempt to disparage this 'single study' was misleading. The study was large, including 1,818 smokers; this sample population was larger than the total combined literature listed by Cochrane for each of three nicotine replacement products marketed by the complainant (nicotine intranasal spray, nicotine inhalator and nicotine sublingual tablet). Since the statistical certainty and projectability of results was directly proportional to the number of cases tested, the NiQuitin CQ Lozenge study stood as an extremely compelling source of evidence.

Lending further weight to the findings from the NiQuitin CQ pivotal study, was the fact that it was conducted on a broad and heterogeneous population of smokers in two continents (in the UK and the US) involving 15 research sites, more than would have participated in the investigation of several other products. This helped ensure the generalisability of the findings. Thus GlaxoSmithKline Consumer Healthcare asserted that the study was a strong and scientifically valid indicator of the performance of the NiQuitin CQ Lozenge, and a legitimate basis for claims.

In the second part of the objection, the complainant concluded with the suggestion that in using ORs, GlaxoSmithKline Consumer Healthcare could not claim top parity since there were other individual studies within the Cochrane database with other forms of NRT which demonstrated better ORs over a 6-12 month timescale. GlaxoSmithKline Consumer Healthcare referred to the discussion above, in which it acknowledged that Cochrane did indeed tabulate results from single studies where they constituted the extant body of evidence. The studies that the complainant referred to did not constitute the extant body of evidence. GlaxoSmithKline Consumer Healthcare asserted that since the statistical certainty and projectability of results was directly proportional to the number of cases tested, it would suggest that these studies in isolation did not stand as compelling sources of evidence in the way that the NiQuitin CQ pivotal study did. The complainant had resorted to 'cherry-picking' in attempting to demonstrate that there were studies in the Cochrane database with higher ORs. Where the evidence available for a given form of NRT involved more than one study, it was indeed inappropriate to 'cherry-pick' from within those studies in order to suggest that a given form of treatment offered unsurpassed efficacy. However, where the evidence from a single study constituted the extant body of evidence as was the case with the NiQuitin CQ pivotal study, this did not constitute 'cherry-picking' – rather it constituted a scientifically valid indicator of performance and a legitimate basis for making claims.

Thus, in summary, GlaxoSmithKline Consumer Healthcare believed it appropriate to claim that no other form of NRT had demonstrated superior efficacy to the NiQuitin CQ 4mg Lozenge.

PANEL RULING

The Panel noted that the manuscript to support the claims being challenged was by Schiffman *et al*. It was to be published in the Annals of Internal Medicine. Schiffman *et al* was a double blind, placebo-controlled, randomized clinical study examining the safety and efficacy of NiQuitin 2mg and 4mg in 1818 patients for smoking cessation; the odds of being abstinent after six weeks of treatment were 2.1 to 3.7 times greater among those on active lozenge (2mg and 4mg) than those on placebo. The authors stated that 'both the absolute success rates and the ORs achieved by the nicotine lozenge were in the upper range of those observed in previous studies of other forms of NRT, suggesting that this may be a particularly effective NRT treatment'. The authors also noted that 'definitive conclusions about comparative efficacy would require a randomized head-to-head comparison'.

The Panel noted that Silagy *et al*, the Cochrane meta-analysis of 108 trials in 35,600 smokers, gave ORs for each form of NRT which met the search criteria. The Panel also noted GlaxoSmithKline Consumer Healthcare's submissions that the meta-analysis tabulated results from single studies where they constituted the extant body of evidence and that such analyses had become the premiere way of assembling and evaluating medical evidence.

The Panel considered that the claim created the impression that the NiQuitin CQ Lozenge had been directly compared with all other forms of NRT therapy and that was not so. The heading to the claim, 'Unsurpassed NRT efficacy' compounded the impression given. The Panel also noted Schiffman *et al*'s comments about the need for direct comparative studies in this regard. The Panel considered that the footnote did not negate the impression given; it was an established principle under the Code that an otherwise misleading claim could not be qualified by a footnote. The Panel considered the claim misleading as alleged. Breaches of Clauses 7.2 and 7.3 of the Code were ruled.

The Panel noted that Schiffman *et al* showed that compared to placebo, treatment with active lozenge resulted in a significantly greater 28 day continuous abstinence at 6 weeks both for the 2mg lozenge (46% v 29.7%, OR=2.10, $p<0.0001$) and the 4mg lozenge (48.7% vs 20.8%, OR=3.69, $p<0.0001$). The Cochrane meta-analysis included individual studies with other forms of NRT in which the OR was greater than the OR for NiQuitin Lozenge; ORs for each were provided ranging from 1.66 to 2.27. The Panel considered that this was a difficult area and noted its general comments above regarding Schiffman *et al* and the authors' conclusions.

The Panel considered that given its ruling that the claim was misleading, the data which did not include a direct comparison did not substantiate the claim at issue. A breach of Clause 7.4 was ruled. The Panel considered that the further alleged breach of Clause 7.2 was covered by this ruling.

2 Claim '… with more dependent smokers tripling their chances of successfully quitting with the NiQuitin CQ 4mg Lozenge compared with placebo at 6 months'

This claim was referenced to Data on file GlaxoSmithKline 2000 [Schiffman *et al*] and appeared as the second half of the same sentence as the claim at issue in point 1.

COMPLAINT

Pharmacia was concerned that the efficacy of NiQuitin CQ 4mg Lozenge was exaggerated. Inspection of the data on file showed that the 6 month continuous abstinence rates were: 23.6% (active) vs 10.2% (placebo). This was 2.31 times greater than placebo and did not substantiate the 'tripling' claim of efficacy, breaching Clause 7.2 and Clause 7.10 of the Code. GlaxoSmithKline Consumer Healthcare had substantiated the claim by using ORs. This did not accurately represent the relative number of individuals actually quitting smoking in the clinical trial, as health professionals would expect. The more appropriate end-point, as presented above, was the relative risk (RR). This reflected the actual number of individuals who successfully quit smoking in the active versus placebo group. Pharmacia provided an appendix explaining why it considered RR was more appropriate.

Pharmacia stated that the OR was often used to estimate RR but as percentages increased the OR would not accurately reflect RR. Pharmacia noted that GlaxoSmithKline Consumer Healthcare stated that those individuals who took more than the median dose of NiQuitin CQ 4mg Lozenge were five times more likely to quit. The study results for success were 56.8% NiQuitin CQ v 19.2% placebo and was not five times greater than the placebo group. The RR was 2.96 whereas the OR was erroneous in reflecting the chances of successfully quitting. The RR was the more accurate and appropriate end point to use when making claims between two interventions in a single trial.

RESPONSE

GlaxoSmithKline Consumer Healthcare stated that the complainant had misstated and miscast the claim as referring to direct comparison of the absolute number of quitters (abstinence rates) in each group. The claim was based on the odds or chances of success for smokers. Analysis showed that the odds or chances of success for each individual smoker were three times greater if they were in the active group rather than in the placebo group.

Summaries of effects of quitting were typically cast in terms of odds. Odds differed from simple percentages in that they contrasted the probability of an outcome to the probability of the alternative outcome. Thus, someone who thought they had a good chance of winning a game might say the chances were '3 to 1' they would win. In this case, 3 = chances of winning, 1 = chances of losing, odds = 3/1, or 3. When one contrasted two groups, for example active and placebo, one typically took the ratio of their odds of success. This was the OR and was the predominant way of summarising clinical trials in smoking cessation. In the case of the NiQuitin CQ 4mg Lozenge data, the odds of being a success if one was in the active group were 0.31 (23.6% success/76.4% failure). The odds of success in the placebo group were 0.11 (10.2% success/89.9% failure). Thus the odds or chances of success were approximately 3 times greater for active treatment than for placebo.

It was important to note at this point that the use of ORs was the primary means by which the authoritative review of the efficacy of these medications, the Cochrane review, reported their efficacy. The OR was used because it properly compared the *relative* chances of success in the active group compared to the placebo group, without being sensitive to overall changes in quit rates, which might occur because of changing study populations, adjunctive behavioural counselling, and so on.

GlaxoSmithKline Consumer Healthcare provided general comments on the use of ORs and RR. The company rejected the complainant's assertion that RR was the only appropriate expression of the efficacy of a stop-smoking product. The complainant presented several distracting arguments that did not bear on the question at hand. The OR was the preferred method of expressing treatment effects, and was the most widely used metric in the scientific literature in this area. It should be noted that the systematic reviews conducted by the Cochrane Tobacco Addiction Review Group used the OR as their primary metric. These reviews provided the main evidence base on treatment efficacy for the Smoking Cessation Guidelines for Health Professionals (Raw *et al* 1998). They were also the main treatment efficacy reference source for the Royal College of Physicians Report 'Nicotine Addiction in Britain' (February 2000).

Among the reasons that ORs were preferred over RR was that they were not sensitive to the direction in which the question and answer was phrased. For example, if a treatment (A) had a 20% success rate, and another (B) had a 30% success rate, one might say either that treatment B increased the chances of success by 50% compared with treatment A (30%-20%/20%), or that it decreased the chances of failure by 12.5% compared with treatment A (70%-80%/80%). This oddly asymmetrical result, one which was clearly counterintuitive but also potentially very misleading, made many analysts prefer the OR, which was robust and invariant, however one expressed the outcome. ORs also had the favourable property that they were insensitive to the base percentages; that was, even if the overall success rate rose or fell, the OR remained a constant expression of the differential effect of one treatment against another. This was particularly important because quit rates were falling over time. However, this property was not true of the relative risk. ORs also had other statistical properties that made them the preferred way of expressing treatment

effects and in analysing tables of results (Rudas 1998). Indeed, Rudas (the author) specifically used language such as 'four times more likely' to report an OR of 4. Thus GlaxoSmithKline asserted that it was legitimate to discuss outcomes in terms of the odds of success, and to express treatment effects as ORs.

GlaxoSmithKline Consumer Healthcare stated that it was somewhat surprised by the complainant's rejection of the OR as a metric. The complainant's own advertising made use of the OR in a similar way in the pharmacy press. For example, in Chemist and Druggist, 12 January 2002, the complainant ran a double-page advertisement claiming that 'Nicorette gum has been proven to offer smokers twice the chance of success over willpower alone'. From the Silagy reference provided at the end of the advertisement, this appeared to be based upon the Cochrane Tobacco Addiction Review Group's summary of the effects of nicotine gum, expressed as an OR of 1.66 (presumably rounded upwards). The Cochrane Review in fact showed that the RR or risk ratio for Nicorette compared to placebo was only 1.48. Were Pharmacia's claim to be based upon the RR, it would be false.

PANEL RULING

Schiffman *et al* showed that 23.6% of patients receiving 4mg lozenge and 10.2% receiving placebo were continuously abstinent at 6 months, OR 2.76 [1.89-4.02].

The Panel noted GlaxoSmithKline Consumer Healthcare's submission about the differences between OR and RR. The Panel noted that although the claim at issue gave the impression that a dependent smoker would be three times more likely to have successfully quit smoking with NiQuitin CQ 4mg Lozenges than with placebo at 6 months some readers might assume that it meant that 3 times as many smokers would quit on NiQuitin CQ than on placebo. This was not so. On balance, the Panel considered the claim misleading as the basis of the calculation had not been made sufficiently clear. A breach of Clause 7.2 was ruled.

Given the data the Panel did not consider the claim exaggerated as alleged. No breach of Clause 7.10 was ruled.

3 Claim '… the NiQuitin CQ 2mg Lozenge can more than triple a smoker's chance of quitting compared with placebo'

This claim appeared in the section headed 'The importance of compliance' and was referenced to Data on file.

An asterisk referred the reader to a footnote which read 'OR measured at 6 weeks, users taking more than the median dose (8.2 4mg Lozenges, 6.7 2mg Lozenges per day) during the first two weeks of treatment'.

COMPLAINT

Pharmacia noted that this claim referred to six week data and was concerned that the efficacy of NiQuitin CQ 2mg Lozenge was also exaggerated. An inspection of GlaxoSmithKline Consumer Healthcare's 'Data on file' quoted the following abstinence rates: 57.7% (active) vs 29.9% (placebo). This was 1.92 times greater than placebo which did not substantiate the 'triple' claim; Pharmacia alleged a breach of Clauses 7.2 and 7.10.

Pharmacia also noted its comments on ORs at point 2 above.

RESPONSE

GlaxoSmithKline Consumer Healthcare considered that in making the same confusion as point 2 above, the complainant reached an incorrect conclusion for the reasons previously described.

It was also important that this claim was read in the context of the heading above it. Both claims 3 and 4 were couched in the context of the importance of good compliance with recommended dosing regimes for a given product. This was an important message if the chance of quitting was to be as high as possible with the product concerned. These claims were not intended to demonstrate absolute numbers of individuals successfully quitting, as erroneously suggested by the complainant. Rather, they were intended to show the doctor that patients would have better chances of success if they used the correct minimum dosage.

In support of this claim, GlaxoSmithKline Consumer Healthcare examined the subgroup of 2mg lozenge users who used more than the median number of lozenges during the first two weeks of their quit attempt and compared the odds of success for the active group to the odds of success for the placebo group. The OR was calculated as follows: the odds of success in the active group were 1.36 (57.7% success/42.3% failure); the odds of success in the placebo group were 0.42 (29.9% success/70.1% failure); the odds of success were thus increased 3.2 (1.36/0.42) times if you were in the active group.

GlaxoSmithKline Consumer Healthcare therefore believed that the claim was not misleading or exaggerated. As in point 2, GlaxoSmithKline clearly stated the time-point and population to which the claim referred.

PANEL RULING

The Panel considered that some of its comments at point 2 above were relevant here. The Panel considered that the claim was misleading as the basis of the calculation had not been made sufficiently clear. The Panel noted that it was an established principle that an otherwise misleading claim could not be qualified by a footnote. The claim was misleading as alleged and a breach of Clause 7.2 was ruled.

The Panel did not consider the claim exaggerated as alleged. No breach of Clause 7.10 was ruled on this point.

4 Claim '… smokers who take above the median dose of 8.2 NiQuitin 4mg Lozenges per day can increase their chances of success by over five times compared to placebo'

This claim also appeared in the compliance section and was referenced to Data on file.

An asterisk referred the reader to a footnote which read 'OR measured at 6 weeks, users taking more than the median dose (8.2 4mg Lozenges, 6.7 2mg Lozenges per day) during the first two weeks of treatment.

COMPLAINT

Pharmacia noted that this claim also referred to six week data from GlaxoSmithKline Consumer Healthcare's 'Data on file' and was concerned again that the efficacy of NiQuitin CQ 4mg Lozenge was exaggerated. The actual figures for abstinence were as follows: 56.8% (active) vs 19.2% (placebo) which equated to 2.96 times greater than placebo. This also did not substantiate the efficacy claim; Pharmacia alleged a breach of Clauses 7.2 and 7.10.

Pharmacia also noted its comments on the OR at point 2 above.

RESPONSE

GlaxoSmithKline referred to its comments above on reading the claim in the context of the heading.

This again arose from the same confusion. GlaxoSmithKline Consumer Healthcare followed the same process used in point 3 above, except for this claim it examined the subgroup of 4mg lozenge users who used above the median number of lozenges during the first two weeks of their quit attempt. The OR was calculated as follows: the odds of success in the active group were 1.31 (56.8% success/43.2% failure); the odds of success in the placebo group were 0.24 (19.2% success/80.8% failure); the odds of success were thus increased 5.5 (1.31/0/24) times if you were in the active group.

GlaxoSmithKline Consumer Healthcare therefore believed that the claim was not misleading or exaggerated. As in point 2, above it clearly stated the time-point and population to which the claim referred.

PANEL RULING

The Panel considered that its ruling at point 3 was relevant here. A breach of Clause 7.2 was ruled as alleged.

The Panel did not consider the claim exaggerated as alleged; no breach of Clause 7.10 was ruled.

Complaint received **23 January 2002**

Case completed **12 April 2002**

CASE AUTH/1273/2/02

PRIMARY CARE GROUP PHARMACEUTICAL ADVISER v AVENTIS PHARMA

Telfast mailing

A primary care group pharmaceutical adviser complained about a Telfast (fexofenadine) mailing sent by Aventis Pharma. The front page was headed 'If something's annoying, deal with it fast' and featured promotional claims, while the reverse carried prescribing information for Telfast 120 and Telfast 180. Telfast 120 was licensed for symptomatic relief of hay fever and Telfast 180 was licensed for symptomatic relief of chronic idiopathic urticaria. The claim 'Telfast provides fast and lasting relief of hay fever symptoms' appeared in bold type on the front of the mailing followed by four bullet points, the last of which read 'Telfast 180 provides fast relief of urticaria'. Immediately below this, again in bold type, was the claim 'Telfast gives fast and lasting relief to your budget'. This was followed by a table headed 'What the NHS saves when a patient is changed to Telfast', referenced to a footnote which read 'Telfast 120 compared to desloratadine, loratadine, cetirizine or levocetirizine, from MIMS, November 2001'. If patients were changed from desloratadine/loratadine to Telfast the saving was 17 pence/patient/month; changing from cetirizine to Telfast saved £1.33/patient/month and changing from levocetirizine to Telfast saved 5 pence/patient/month. The bottom right hand corner of the front page featured the Telfast 120 product logo with the strapline 'Fast relief of hay fever'.

The complainant alleged that the mailing implied that there were savings to the NHS budget which was misleading as Telfast was more expensive for treating urticaria. The bullet point immediately above the claim 'Telfast gives fast and lasting relief to your budget' referred to urticaria, where only the more expensive medicine was licensed. The NHS only saved when treating hay fever. The indication of urticaria was given undue prominence.

The Panel noted that with one exception all of the claims on the mailing appeared to relate to Telfast 120; however the last bullet point beneath the claim 'Telfast provides fast and lasting relief of hayfever symptoms' read 'Telfast 180 provides fast relief of urticaria' thus introducing the other presentation. This was immediately followed by the claim 'Telfast gives fast and lasting relief to your budget'. Given that in this claim the presentation of Telfast had not been specified and that it was preceded by claims about hay fever and about urticaria, some readers might assume that the savings shown related to both Telfast 120 and Telfast 180 which was not so. The savings only related to the use of Telfast 120. Although this was stated in the footnote to the table the Panel noted that it was an accepted principle under the Code that otherwise misleading statements could not be qualified by the small print. Changing patients from desloratadine, loratadine, cetirizine or levocetirizine to Telfast 180 for urticaria would increase prescribing costs. The Panel considered that the mailing was misleading and a breach of the Code was ruled.

A primary care group pharmaceutical adviser complained about a Telfast (fexofenadine) mailing (ref TEL1281201) sent by Aventis Pharma Ltd. The mailing consisted of a single A5 sheet printed on both sides. The front of the mailing was headed 'If something's annoying, deal with it fast' and featured promotional claims for the product while the reverse carried the prescribing information for Telfast 120 and Telfast 180. Telfast 120 was licensed for symptomatic relief of hay fever and Telfast 180 was licensed for symptomatic relief of chronic idiopathic urticaria.

The claim 'Telfast provides fast and lasting relief of hay fever symptoms' appeared in bold type on the front of the mailing followed by four bullet points, the last of which read 'Telfast 180 provides fast relief of urticaria'. Immediately below this, again in bold type, was the claim 'Telfast gives fast and lasting relief to your budget'. This was followed by a table of data which showed 'What the NHS saves when a patient is changed to Telfast'. This was referenced to a footnote which was beneath the table and read 'Telfast 120 compared to desloratadine, loratadine, cetirizine or levocetirizine, from MIMS, November 2001'. If patients were changed from desloratadine/loratadine to Telfast the saving was 17 pence/patient/month; changing from cetirizine to Telfast saved £1.33/patient/month and changing from levocetirizine to Telfast saved 5 pence/patient/month. The bottom right hand corner of the front page featured the Telfast 120 product logo with the strapline 'Fast relief of hay fever'.

COMPLAINT

The complainant stated that the mailing implied that there were savings to the NHS budget which was misleading as Telfast was more expensive for treating urticaria. The bullet point immediately above the claim 'Telfast gives fast and lasting relief to your budget' referred to urticaria, where only the more expensive medicine was licensed. The NHS only saved when treating hay fever. The indication of urticaria was given undue prominence.

When informing Aventis of the complaint the Authority requested that it consider the requirements of Clause 7.2 of the Code.

RESPONSE

Aventis submitted that it did not at any point claim that the NHS would save when prescribing the Telfast 180mg dose, and therefore the claim was not in any way misleading.

The two featured claims in the mailing were 'Telfast provides fast and lasting relief of hay fever symptoms' followed by 'Telfast gives fast and lasting relief to your budget'. As they were in bold type, it was clear that the information below related to the headings ie in hay fever. In addition to this, the comparison in the table referred to was further clarified by the addition of the footnote: 'Telfast 120 compared to desloratadine, loratadine, cetirizine or levocetirizine, from MIMS, November 2001'.

Aventis considered that this table provided a clear, factually correct and accurate representation of the cost of the medicines mentioned.

Aventis did not agree with the complainant's view that the indication of urticaria was given undue prominence. The mailing contained the two bold claims detailed above and a number of bullet points. The statement relating to urticaria was given no more prominence than any other bullet point, and less than the claims that were in bold type.

In Aventis' view the mailing was not in breach of Clause 7.2 of the Code.

PANEL RULING

There were two presentations of Telfast; Telfast 120 for symptomatic relief of hayfever and Telfast 180 for symptomatic relief of chronic idiopathic urticaria. The Telfast 120 product logo appeared in the bottom right hand corner of the front of the mailing and one of the prominent claims referred to relief of hay fever symptoms. A footnote to the table showing the money to be saved when changing a patient to Telfast specified that the data related to Telfast 120. Most of the product references, however, were to Telfast with no suffix to distinguish between the two presentations.

With one exception all of the claims on the mailing appeared to relate to Telfast 120; however the last bullet point beneath the claim 'Telfast provides fast and lasting relief of hayfever symptoms' read 'Telfast 180 provides fast relief of urticaria' thus introducing the other presentation. This was immediately followed by the claim 'Telfast gives fast and lasting relief to your budget'. Given that in this claim the presentation of Telfast had not been specified and that it was preceded by claims about hay fever and about urticaria, some readers might assume that the savings shown related to both Telfast 120 and Telfast 180 which was not so. The savings only related to the use of Telfast 120. Although this was stated in the footnote to the table the Panel noted that it was an accepted principle under the Code that otherwise misleading statements could not be qualified by the small print. The Panel noted that changing patients from desloratadine, loratadine, cetirizine or levocetirizine to Telfast 180 for urticaria would increase prescribing costs. The Panel considered that the mailing was misleading and a breach of Clause 7.2 was ruled.

Complaint received	**6 February 2002**
Case completed	**22 March 2002**

CASE AUTH/1274/2/02

MERCK SHARP & DOHME v PFIZER

Promotion of Lipitor

Merck Sharp and Dohme complained about a Lipitor (atorvastatin) letter produced by Pfizer which discussed evidence from the Heart Protection Study (HPS) regarding the benefits of statin treatment. The statin used in the HPS was simvastatin marketed by Merck Sharp & Dohme as Zocor. The letter also discussed the potential cost savings from a Lipitor price reduction.

The claim 'Growing evidence supporting wider use of statins' appeared as the heading to the letter, it was then stated that the HPS demonstrated lowering cholesterol reduced heart attacks and strokes by a third in all patients at high risk of cardiovascular disease (CVD). Merck Sharp and Dohme alleged this to be misleading and intended to suggest that Lipitor was indicated in such patients. Lipitor was not indicated for prevention of CVD or stroke, and such promotion was outside its licence.

The Panel noted that the HPS assessed the effects of cholesterol-lowering therapy (simvastatin) and of antioxidant vitamin supplementation in various patient categories. Simvastatin produced reductions in major vascular events of at least one-third in a very wide range of high-risk patients for whom there had previously been uncertainty about using cholesterol-lowering therapy.

According to its summary of product characteristics (SPC) Lipitor was indicated as an adjunct to diet to lower plasma lipids in patients with various types of hypercholesterolaemia or hyperlipidaemia.

The Panel noted that simvastatin (Zocor) rather than atorvastatin (Lipitor) was administered in the HPS. The initial paragraphs of the letter mentioned statins as a class; there was no mention of Zocor. The relevant paragraphs appeared immediately above and adjacent to a table headed 'Lipitor price reduction and potential cost savings'. Subsequent paragraphs discussed Lipitor; the final paragraph on the first page referred to cost savings if Lipitor was prescribed rather than Zocor as used in the study. Nonetheless, the Panel considered that it had not been made clear that simvastatin rather than Lipitor had been used in the HPS. Lipitor was not licensed for reduction of the risk of heart attacks and strokes. The Panel considered that the section would mislead as to the licensed indications for Lipitor and this was inconsistent with the Lipitor SPC. A breach of the Code was ruled.

The claim 'LIPITOR price cut to help meet new statin demand' appeared as a subheading to the third paragraph of the letter, beneath the section at issue above. This section included the words 'new statin demand' in conjunction with the comment that the 'price of Lipitor has been reduced to enable more patients to be treated'. Merck Sharp & Dohme considered this clearly inferred that the same type of patients as those included in the HPS could now potentially be placed on treatment with Lipitor and expect a benefit from treatment. Merck Sharp & Dohme alleged that this was misleading and outside the licence.

The Panel considered that the claim at issue would be read in light of the preceding paragraph; the 'new statin demand' referring to the patient population in HPS. The claim implied that the purpose of the price reduction was to encourage use of Lipitor in the patient population examined in HPS, including those without hypercholesterolaemia. The Panel ruled that the claim was inconsistent with the Lipitor SPC and in breach of the Code.

The claim 'Lipitor 10mg provides similar LDL-cholesterol reductions to Zocor 40mg' appeared in the section headed by the claim at issue above. This comparison was made following a statement that should primary care organisations wish to see similar reductions in LDL-cholesterol as seen in the HPS (when Zocor 40mg was used), then by using Lipitor 10mg cost savings could be made. Merck Sharp and Dohme considered that the implication was that Lipitor 10mg was as efficacious in lowering LDL-cholesterol as Zocor 40mg and this comparison was referenced to the CURVES study. In the CURVES study, a comparison of doses was made but the changes to the lipid profiles clearly demonstrated that Lipitor 10mg was comparable to 20mg of simvastatin; the changes seen with 40mg of simvastatin were better than those seen with atorvastatin 10mg; other comparative studies confirmed this. Merck Sharp & Dohme therefore alleged that this was misleading and disparaging of the effects seen with Zocor 40mg.

The Panel noted that the claim was referenced to Jones *et al* (1998), the CURVES study, in which it was concluded that Lipitor 10mg produced greater reductions in LDL-cholesterol than simvastatin 10mg as against baseline. However the percentage change in LDL-cholesterol achieved by simvastatin 40mg versus Lipitor 10mg was not statistically significant.

The Panel noted Pfizer's submission that it did not state that Lipitor 10mg was as efficacious as simvastatin 40mg in the CURVES study but rather that the magnitude of the LDL-cholesterol reduction in the CURVES study was comparable to that achieved by 40mg simvastatin in the HPS baseline paper and the CURVES study.

The Panel noted that the claim at issue was preceded by a statement that 'Primary Care Organisations seeking to reduce LDL-cholesterol levels by the 1-1.5mmol/L seen in the HPS could now save over £150,000 per year for every thousand statin patients, simply by prescribing Lipitor 10mg rather than the Zocor 40mg used in the study'. The Panel did not consider that the claim at issue was misleading as alleged; the claim related to LDL-cholesterol reduction and was not unreasonable given the data in the CURVES study. The Panel ruled no breach of the Code.

The claim 'Achieving the minimum standard requires use of either Lipitor 10 mg … or Zocor

20mg' appeared in a section headed 'Major cost savings can be made' which discussed the National Service Framework (NSF) advice that LDL cholesterol must be lowered by at least 30% in all patients at high risk of CHD.

Merck Sharp & Dohme alleged that this was a highly disparaging and misleading claim, implying that only two statins, and specific doses of those statins, could reduce LDL-cholesterol to the minimum standard required to achieve the NSF target for CHD, once more referenced to the CURVES study. This was not a fair reflection of the current data for all prescribable statins at different strengths.

The Panel considered that the claim implied that only Lipitor 10mg and simvastatin 20mg could achieve the required reduction. It was a strong claim; the term 'required' implied that only the two statins mentioned at the doses stated would satisfy. On balance the Panel considered that the claim was misleading as alleged. A breach of the Code was ruled.

Merck Sharp and Dohme Limited complained about a Lipitor (atorvastatin) letter (reference CS32-2954cr 10/01) produced by Pfizer Limited and sent to health professionals on 13 December 2001. Merck Sharp & Dohme marketed Zocor (simvastatin).

The letter discussed evidence from the Heart Protection Study (2001) (HPS) regarding the benefits of statin treatment. The study had been funded, in part, by the UK Medical Research Council and the British Heart Foundation. The statin used in the HPS was simvastatin. The letter also discussed the potential cost savings from a Lipitor price reduction.

1 Claim 'Growing evidence supporting wider use of statins'

This claim appeared as the heading to the letter.

COMPLAINT

Merck Sharp and Dohme noted that the first paragraph of the letter stated that evidence from the HPS highlighted the fact that many thousands more patients could potentially benefit from statin treatment. The letter then stated that the HPS demonstrated that lowering cholesterol reduced heart attacks and strokes by a third in all patients at high risk of cardiovascular disease (CVD). Merck Sharp and Dohme alleged this to be misleading and intended to suggest to physicians that Lipitor was indicated in such patients. Lipitor was not indicated for the prevention of CVD or stroke, and promotion in this way was outside its licence.

In intercompany correspondence Pfizer had claimed that this section merely illustrated the growing body of evidence suggesting a benefit for reducing cholesterol and had quoted a number of other papers which had demonstrated this. However, despite quoting a number of references, it failed to use these within the letter at issue, instead choosing to focus on the findings of one study, the HPS. The section immediately following in the letter, only illustrated that existing patients with coronary heart disease (CHD) were being inadequately treated with statins. There was no clarification of the current licensed indications for Lipitor. This section had the potential to mislead clinicians into believing that Lipitor was indicated to reduce the risk of heart attacks and stroke thus a breach of Clause 3.2 of the Code was alleged.

RESPONSE

Pfizer stated that the HPS was a UK study and was presented for the first time at the American Heart Association (AHA) meeting in November 2001. At the time the letter at issue was distributed, there had been a considerable amount of general and medical media interest in the study and therefore, it seemed appropriate to mention it in this one-off communication with physicians.

Pfizer did not agree that it was suggesting that atorvastatin was indicated for the prevention of heart attacks or stroke. Pfizer did not make any claims to this effect, but rather pointed out that there was increasing evidence to suggest a benefit for reducing cholesterol for which atorvastatin was licensed. Recent meta-analyses in patients with CHD (LaRosa 1999 and Gould *et al* 1998) and diabetes (Huang *et al* 2001), as well as recent analyses of another landmark study (Pederson 1998), had repeatedly confirmed the benefits of lowering cholesterol with statins, and this benefit appeared to be directly proportional to the degree to which they lowered lipids (Gould *et al*).

The letter at issue discussed Hippisley-Cox and Pringle (2001) which concluded that patients with established CHD (who were therefore at high risk of a subsequent event) were not being treated appropriately with statins. In this analysis, the majority of the primary-care patients remained hypercholesterolaemic (total cholesterol>5mmol/l) despite statin therapy. This would support Pfizer's assertion that there was growing evidence to support wider use of statins.

The HPS (with its aim to reduce cholesterol by 1-1.5mmol/l over 5 years) added to the growing body of evidence that the benefit of statins was related to the ability to lower cholesterol levels (for which atorvastatin did have a licence). In the letter at issue Pfizer did not claim that it had a licence to prevent the risk of heart attacks or stroke, and therefore did not consider it was promoting outside its licence, in breach of Clause 3.2 of the Code.

PANEL RULING

The Panel noted that the HPS, published in abstract format, assessed the effects of cholesterol-lowering therapy (simvastatin) and of antioxidant vitamin supplementation in various patient categories (n=20,536) for which there had been uncertainty about the value of such treatment. Patients aged 40-80 with a history of occlusive vascular disease or diabetes were eligible provided their own doctors did not consider statin therapy clearly indicated. Among the 7150 patients with no history of CHD, 1820 reported a previous stroke or transient ischaemic attack, 2701 reported some other peripheral artery disease and 3982 were diabetics. Total cholesterol was <5.0mmol/1 (194mg/dl) in 4072 patients and LDL-cholesterol was <3.0mmol/l (116mg/dl) in 6793 patients.

Participants were randomly allocated simvastatin 40mg daily or matching placebo for 5½years. Simvastatin reduced total and vascular mortality, total CHD, stroke and revascularisation procedures with no good evidence of any effect on non-vascular mortality or cancer. Simvastatin 40mg produced reductions in major vascular events of at least one-third in a very wide range of high-risk patients for whom there had previously been uncertainty about using cholesterol-lowering therapy, including woman, people aged over 70, those with LDL-cholesterol below 3.0mmol/l and those with diabetes or non-coronary occlusive disease without pre-existing CHD.

The Panel noted that according to its summary of product characteristics (SPC) Lipitor was indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other non-pharmacological measures was inadequate. Lipitor also raised HDL and lowered the LDL/HDL and total cholesterol/HDL ratios. Lipitor was also indicated as an adjunct to diet and other non-dietary measures in reducing elevated total cholesterol, LDL-cholesterol and apolipoprotein B in patients with homozygous familial hypercholesterolaemia when response to these measures was inadequate.

The Panel noted that simvastatin (Zocor) rather than atorvastatin (Lipitor) was administered in the HPS. When discussing the HPS the initial paragraphs of the letter at issue mentioned statins as a class; there was no mention of Zocor. The relevant paragraphs appeared immediately above and adjacent to a table headed 'Lipitor price reduction and potential cost savings'. Subsequent paragraphs discussed Lipitor; the final paragraph on the first page stated that primary care organisations seeking to reduce LDL-cholesterol levels by the 1-1.5mmol/l seen in the HPS could now save £150,000 per year for every thousand statin patients simply by prescribing Lipitor 10mg rather than Zocor 40mg used in the study. Nonetheless, in the context of a promotional item for Lipitor the Panel considered that it had not been made clear that simvastatin rather than Lipitor had been used in the HPS. Lipitor was not licensed for reduction of the risk of heart attacks and strokes. The Panel considered that the section would mislead as to the licensed indications for Lipitor and this was inconsistent with the Lipitor SPC. A breach of Clause 3.2 of the Code was ruled.

2 Claim 'LIPITOR price cut to help meet new statin demand'

This claim appeared as a subheading to the third paragraph of the letter, beneath the section at issue at point 1 above.

COMPLAINT

Merck Sharp & Dohme stated that in relation to the HPS, the mailing had already highlighted that many more thousands of people could benefit from treatment with a statin. The fact that this section of the letter included the words 'new statin demand' in conjunction with the comment that the 'price of Lipitor has been reduced to enable more patients to be treated' clearly inferred that the same type of patients as those included in the HPS could now potentially be placed on treatment with Lipitor and expect a benefit from treatment. Merck Sharp & Dohme alleged that this was misleading to clinicians and promoted outside of the licence in breach of Clause 3.2 of the Code, as the HPS patients included diabetics, hypertensives etc who did not have hypercholesterolaemia, the current licensed indication for Lipitor.

RESPONSE

Pfizer stated that the National Service Framework for CHD highlighted the targets of total cholesterol <5mmol/l (or by 20-25% whichever was greater), LDL-cholesterol <3mmol/l (or by 30% whichever was greater) (data on file). In the letter at issue it mentioned Hippisley-Cox and Pringle (2001) which concluded that two/thirds of CHD patients in their survey had a cholesterol>5mmol/l, even though many were taking some sort of lipid-lowering agent. It was this need to which Pfizer was referring in its letter to health professionals. Other data supporting this message of an unmet need in the management of lipid levels in CHD patients included the following publications:

- A primary care UK study in which 24,000 patients with CHD from 550 UK general practices were surveyed in 1997 and 1998. 35% of men and 52% of women did not have a cholesterol recorded, while 47% of men and 40% of women had a total cholesterol>5mmol/l. Only 18% of men and 13% of women with CHD were on statins (Brady *et al* 2001).
- At a European level, Euroaspire 2 (2001) collected data in 1999 and 2000 on 3,000 CHD patients in hospitals in 9 European countries, excluding the UK. It found that 60% had cholesterol over 5.0mmol/l, with a quarter with cholesterol over 6.0mmol/l. Two-thirds of all people with CHD were on cholesterol-lowering therapy, but only a half reached a target of 5mmol/l or less.
- PRAIS-UK (Arnada *et al* 1994). In this prospective cohort registry study, 56 UK hospitals serving approximately 14 million people enrolled 1046 patients with acute coronary syndrome (ACS), or patients with ECG changes consistent with myocardial ischaemia and/or a history of coronary artery disease. In this cohort 62% of the patients had a total cholesterol measured during their admission, and around 50% of all the patients with ACS and a cholesterol> 6mmol/l were not receiving a statin at 6 months.

Pfizer stated that these data confirmed that there were thousands of new patients with CHD and cholesterol levels >5mmol/l who would benefit from lipid-lowering with statin therapy.

Additionally in the HPS baseline paper (1999), it was reported that 66% of the patients had a baseline LDL-cholesterol of >3mmol/l and 62% had a total cholesterol of >5.5mmol/l.

In the letter at issue Pfizer did not mention patients with a 'normal' cholesterol level or any other condition (diabetics/hypertensives), and therefore did not consider that it was promoting outside its licence, or that it was in breach of Clause 3.2 of the Code.

PANEL RULING

The Panel considered that the claim at issue would be read in light of the preceding paragraph; the 'new statin demand' referring to the patient population in HPS. The Panel considered that the claim at issue implied that the purpose of the price reduction was to encourage use of Lipitor in the patient population examined in HPS, including those without hypercholesterolaemia. The Panel considered that the claim was inconsistent with the Lipitor SPC contrary to the requirements of Clause 3.2 of the Code; a breach of that clause was ruled.

3 Claim 'Lipitor 10mg provides similar LDL-cholesterol reductions to Zocor 40mg'

This claim appeared in the section headed by the claim at issue in point 2 above.

COMPLAINT

Merck Sharp and Dohme stated that this comparison was made following a statement that should primary care organisations wish to see similar reductions in LDL-cholesterol as seen in the HPS (when Zocor 40mg was used), then by using Lipitor 10mg cost savings could be made. The implication was that Lipitor 10mg was as efficacious in lowering LDL-cholesterol as Zocor 40mg and this comparison was referenced to the CURVES study. In the CURVES study, a comparison of doses was indeed made but the changes to the lipid profiles clearly demonstrated that Lipitor 10mg was comparable to 20mg of simvastatin; the changes seen with 40mg of simvastatin were better than those seen with atorvastatin 10mg, other comparative studies confirmed this (Dart *et al* 1997).

This was therefore misleading to physicians and disparaging of the effects seen with Zocor 40mg in breach of Clause 7.3 of the Code.

RESPONSE

Pfizer pointed out that it did not state that atorvastatin 10mg was as efficacious as simvastatin 40mg in the CURVES study – but rather that the magnitude of reduction of LDL-C (38% for 10mg Lipitor) in CURVES was similar/comparable to that reported with 40mg simvastatin in the HPS baseline paper and the CURVES study. Pfizer did not believe that it was disparaging the effects of simvastatin 40mg and did not believe that it was in breach of Clause 7.3 of the Code. In the baseline HPS (1999) the percentage of total and LDL-cholesterol reduction achieved by simvastatin 40mg during the pre-randomization phase of HPS was reported. Patients with an LDL-cholesterol at baseline of <3.5mmol/l achieved a 39% reduction whilst those with a baseline >3.5mmol/l achieved a 37% reduction in LDL-cholesterol. The LDL-cholesterol reduction noted in this study for 40mg simvastatin was consistent with a meta-analysis of statins by Hilleman *et al* (1999) where the LDL-cholesterol reduction for simvastatin 40mg was 38.8%, and in the Stein *et al* (1998) study where the LDL-cholesterol reduction was 38% with simvastatin 40mg.

In Merck Sharp and Dohme's analysis of CURVES it mentioned that simvastatin 40mg was 'better' than Lipitor 10mg, which was 'comparable' to 20mg simvastatin. Review of the paper showed that the difference between 10mg Lipitor and 40mg simvastatin (3% difference LDL-cholesterol reduction ie 38 and 41% respectively) was the same as that between 10mg Lipitor and 20mg simvastatin (3% difference LDL-cholesterol reduction 38 and 35% respectively). The level of LDL-cholesterol reduction seen with Lipitor 10mg in CURVES (38%) was consistent and 'similar' to that quoted in a recent review 35–42% and the aforementioned meta-analysis – 36.6%.

Pfizer did not understand Merck Sharp and Dohme's reference to Dart *et al* (1997) which compared 10 and 20mg of Lipitor and simvastatin, and showed Lipitor produced 'significantly greater reductions from baseline than did simvastatin for LDL-cholesterol, total cholesterol, VLDL, TG and Apo B' at 16 weeks. Further review of the paper showed that in the patients on Lipitor at 52 weeks, the mean reduction in LDL-cholesterol was 38% while the patients on simvastatin achieved a 33% reduction in LDL-cholesterol ($p \leq 0.0036$ in favour of Lipitor). In another study (Farnier *et al*, 2000) comparing Lipitor and simvastatin the LDL-cholesterol reduction seen with 10mg Lipitor was 37% compared to 33.8% for simvastatin 20mg and 28.9% for simvastatin 10mg. Karalis *et al,* a poster presentation at the 72nd European Atherosclerosis Society congress, demonstrated that 10mg of Lipitor reduced LDL-cholesterol by 37.1% while 20mg simvastatin achieved a reduction of 35.4% ($p=0.0097$).

PANEL RULING

The Panel noted that the claim at issue was referenced to Jones *et al* (1998), the CURVES study, which examined the comparative dose efficacy of Lipitor versus simvastatin, pravastatin, lovastatin and fluvastatin in patients with hypercholesterolemia. The study concluded, *inter alia*, that Lipitor 10mg produced greater ($p \leq 0.001$) reductions in LDL-cholesterol than simvastatin 10mg as against baseline. However the percentage change in LDL-cholesterol achieved by simvastatin 40mg versus Lipitor 10mg was not statistically significant; –41% versus –38% respectively. The authors noted that the CURVES study in conjunction with previous comparative studies that had included Lipitor had clearly established Lipitor as the most efficacious statin for lowering LDL-cholesterol.

The Panel noted Pfizer's submission that it did not state that Lipitor 10mg was as efficacious as simvastatin 40mg in the CURVES study but rather that the magnitude of the LDL-cholesterol reduction

in the CURVES study was comparable to that achieved by 40mg simvastatin in the HPS baseline paper and the CURVES study.

The Panel noted that the claim at issue was preceded by a statement that 'Primary Care Organisations seeking to reduce LDL-cholesterol levels by the 1-1.5mmol/L seen in the HPS could now save over £150,000 per year for every thousand statin patients, simply by prescribing Lipitor 10mg rather than the Zocor 40mg used in the study'. The Panel did not consider that the claim at issue was misleading as alleged; the claim related to LDL-cholesterol reduction and was not unreasonable given the data in the CURVES study. The Panel ruled no breach of Clause 7.3.

4 Claim 'Achieving the minimum standard requires use of either Lipitor 10 mg … or Zocor 20mg'

The claim appeared in a section headed 'Major cost savings can be made' which discussed the National Service Framework (NSF) advice that LDL cholesterol must be lowered by at least 30% in all patients at high risk of CHD.

COMPLAINT

Merck Sharp & Dohme alleged that this was a highly disparaging claim, implying that only two statins, and specific doses of those statins, could reduce LDL-cholesterol to the minimum standard required to achieve the NSF target for CHD, once more referenced to the CURVES study. This was not a fair reflection of the current data for all prescribable statins at different strengths.

Dart *et al* compared the effects of simvastatin 10mg and Lipitor 10mg. After 16 weeks of treatment, a mean reduction of LDL-cholesterol of 37% was achieved by 10mg of atorvastatin but simvastatin 10mg achieved a 30% mean reduction which met the current NSF requirement as quoted in this letter. Merck Sharp & Dohme alleged that the claim was misleading and in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Pfizer stated this statement needed to be taken in context with rest of the letter that was clearly a comparison of Lipitor and simvastatin. Simvastatin was currently the market leading statin in the UK, while Lipitor and simvastatin together accounted for around 80% of the entire UK statin market. In earlier correspondence with Merck Sharp and Dohme, Pfizer agreed in principle to reissue a price mailing with a comparison with all the prescribable statins at all doses; Merck Sharp & Dohme did not ask it to re-issue such a price mailing, and therefore Pfizer was disappointed that Merck Sharp & Dohme had taken this further.

With regard to the Dart study, in the 45 patients who received 10mg simvastatin the mean LDL-cholesterol reduction was 30% after 16 weeks. However, there were several other studies and a meta-analysis, where the level of LDL-cholesterol reduction was consistent with that seen for simvastatin 10mg in the Curves analysis, and did not achieve 30% reduction. For this reason Pfizer did not consider that it was in breach of either Clauses 7.2 or 7.3 of the Code.

PANEL RULING

The Panel noted that the claim at issue appeared in a promotional item comparing Lipitor and simvastatin; nonetheless the Panel considered that the claim implied that only Lipitor 10mg and simvastatin 20mg could achieve the required reduction. It was a strong claim; the term 'required' implied that only the two statins mentioned at the doses stated would satisfy. On balance the Panel considered that the claim was misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **6 February 2002**

Case completed **15 April 2002**

CASE AUTH/1275/2/02

VOLUNTARY ADMISSION BY ASTRAZENECA

Breach of undertaking

AstraZeneca voluntarily advised the Authority that an advertisement for Nexium (esomeprazole) that had been ruled in breach of the Code in Case AUTH/1237/10/01 had been used again in error and had appeared in Pulse.

The Director of the Authority decided that the matter was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The Panel noted that Case AUTH/1237/10/01 had involved a number of different advertisements which all featured a high jumper with the impression of wings added and the ground appearing hundreds of feet below. Each advertisement was headed 'Expect more. Achieve more' with text lower down stating 'Nexium heals more reflux oesophagitis patients than lansoprazole'. Breaches of the Code had been ruled and the case had been completed in December 2001.

AstraZeneca submitted that following its acceptance of the Panel's ruling it had instructed its advertising agency to stop all medical journals from running the original advertisement. Pulse's reproduction house had used an old printing plate instead of the new one.

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

The Panel noted that AstraZeneca had ensured that its advertising agency knew that the original advertisement was no longer to be used; new films and copy instructions were issued but AstraZeneca appeared not to have issued any instructions to ensure that the old material was destroyed by the agency or returned to the company for destruction. The advertisement at issue had appeared approximately eight weeks after the completion of the previous case due to the use of an old printing plate that had been left with the journal's reproduction house. As a consequence AstraZeneca had failed to comply with its undertaking. A breach of the Code was ruled as acknowledged by AstraZeneca.

Taking all the circumstances into account, the Panel considered that despite AstraZeneca voluntarily bringing the matter to the attention of the Authority, the failure to ensure that the plates were destroyed constituted a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

COMPLAINT

AstraZeneca UK Limited advised the Authority that an advertisement for Nexium that had been ruled in breach of the Code (Case AUTH/1237/10/01) had been used again in error. The advertisement had appeared in Pulse on 11 February.

The Director of the Authority decided that the matter was sufficiently serious for it to be taken up and dealt with as a formal complaint under the Code. This was consistent with advice given by the Code of Practice Appeal Board and published in the August 1997 Code of Practice Review.

The Authority requested that, when considering the matter, AstraZeneca respond in relation to the provisions of Clauses 2, 9.1 and 22 of the Code.

RESPONSE

AstraZeneca stated that the advertisement that was the subject of Case AUTH/1237/10/01 reappeared in Pulse on 11 February, due to an error caused by the journal's reproduction house.

The actions taken by AstraZeneca following the rulings in Case AUTH/1237/10/01 were outlined.

30 November – AstraZeneca received written notification of the Panel's ruling.

14 December – After studying the ruling AstraZeneca requested clarification in order to understand the implication of the requirements needed to comply fully with any undertaking. AstraZeneca also requested to be given an extension until 20 December to respond to the ruling in view of the disruption caused through its office move. AstraZeneca made contingency plans for the event that the Authority's feedback did not give the clarity AstraZeneca was seeking. These plans included running the existing advertisement without any strapline or text.

20 December – The Authority provided written feedback to AstraZeneca. AstraZeneca then invoked the contingency plan and instructed the advertising agency to produce the revised (interim) advertisements that were to include just the Nexium visual and logo. The strapline and claim that were the subjects of the ruling in Case AUTH/1237/10/01 were to be removed. AstraZeneca explained to the advertising agency that the ruling had been accepted and therefore instructed the advertising agency to stop all medical journals from running the original advertisement forthwith subject to the publication copy deadline of the journal. Due to imminent Christmas holidays some of the publication deadlines had already passed and as a consequence, where it was not possible to meet the copy deadline for the next issue, the advertising agency gave clear instructions to all journals running Nexium advertisements to replace the advertisement in subsequent editions when the new advertisement was received. This was executed by phone calls to the production department of journals and through copy instructions sent with each batch of new films. The new films and copy instructions were all delivered within the copy deadlines set by the journals.

The advertising agency supplied a list to AstraZeneca of journal advertisements that could not be altered and this was used as the basis of the date of 31

January for the last appearance of the advertisement, which was then cited in the letter of undertaking and provided to the Authority on 20 December, after all necessary measures had been taken.

Events leading to the advertisement reappearing were outlined:

21 December – Advertising agency submitted interim advertisements to AstraZeneca for copy approval. This advertisement ran in Pulse editions in January.

5 February – Artwork for a new size interim advertisement was sent to Pulse (for a copy date of 6 February) with full copy instructions as to when the advertisement was to run.

11 February – The advertising agency informed AstraZeneca that the original Nexium advertisement had appeared in Pulse, 11 February. The advertising agency forwarded email correspondence from Pulse admitting responsibility for an error at its reproduction house where an old printing plate had been used instead of the new one.

AstraZeneca conducted an initial investigation to confirm that the error had occurred as the result of a third party and immediately requested the advertising agency to contact Pulse and all other medical journals used in the Nexium advertising campaign to ensure that the incident could not be repeated.

13 February – AstraZeneca informed the Authority of the error.

An illustration of the standard procedure used by the advertising agency when dealing with AstraZeneca and other pharmaceutical companies for the production of advertisements in journals was provided.

AstraZeneca believed that this showed the complexity of the procedure which was similar to that used throughout the industry and which involved six different parties of whom AstraZeneca had direct contact with two (the advertising agency and the media buyer). The complexity of the procedure would certainly appear likely to increase the risk of third party human error, an example of which occurred in this instance.

AstraZeneca believed that it took all reasonable measures to ensure compliance with the undertaking. The reappearance of the advertisement occurred as a consequence of an error by a third party ie the reproduction house for Pulse for which Pulse had apologised. Indeed despite having the revised advertisement run in 26 different journals and in 32 formats, the only error had occurred with Pulse.

AstraZeneca therefore accepted that there had been a breach of Clause 22 but denied any breach of Clause 9.1 or Clause 2.

AstraZeneca submitted that it had behaved responsibly by voluntarily bringing this matter to the attention of the Authority. In further support of this, AstraZeneca cited past precedents of two similar cases where ultimately a breach of Clause 2 was not ruled (Cases AUTH/1028/6/00 and AUTH/1087/10/00).

AstraZeneca trusted that the case would be viewed on the evidence presented and that the error that occurred was in spite of the full level of care and commitment to complying with the undertaking that AstraZeneca always applied in such cases.

PANEL RULING

In Case AUTH/1237/10/01 Wyeth had complained about journal advertisements for Nexium (esomeprazole) issued by AstraZeneca. There were a number of variations in the layout of the advertisements but all featured a high jumper with the impression of wings added and the ground appearing hundreds of feet below. Each advertisement was headed 'Expect more. Achieve more' with text lower down stating 'Nexium heals more reflux oesophagitis patients than lansoprazole'. The Panel had ruled breaches of Clauses 7.2 and 7.3 of the Code. Case AUTH/1237/10/01 was completed in December 2001. AstraZeneca submitted that following its acceptance of the Panel's ruling it had instructed its advertising agency to stop all medical journals from running the original advertisement. The Pulse reproduction house had used an old printing plate instead of the new one.

Turning to the case now before it, Case AUTH/1275/2/02, the Panel considered that an undertaking was an important document. It included an assurance that all possible steps would be taken to avoid similar breaches of the Code in the future. It was very important for the reputation of the industry that companies complied with undertakings.

The Panel noted the cases referred to by AstraZeneca. In Case AUTH/1087/10/00 the Panel's ruling of a breach of Clause 2 had been overturned by the Appeal Board on appeal. This case concerned an advertisement used three months after it had been ruled in breach of the Code. The company had issued new material but unusual circumstances at its advertising agency led to the original advertisement being reprinted. Case AUTH/1028/6/00, which also arose as the result of a voluntary admission, concerned the use of a claim similar to one that had been ruled in breach of the Code. The company concerned had instructed that all materials should be destroyed. Advertising film plates had subsequently been recalled by its current advertising agency. A journal had however, used an old plate which had been left with it by a previous advertising agency. No breach of Clause 2 was ruled. In the Panel's view the circumstances in the case now before it were different to those in the cases referred to by AstraZeneca.

The Panel noted that the AstraZeneca procedure had ensured that its advertising agency knew that the original advertisement was no longer to be used; new films and copy instructions were issued but AstraZeneca appeared not to have issued any instructions to ensure that the old material was destroyed by either the agency or returned to the company for destruction. The advertisement at issue had appeared approximately eight weeks after the completion of the previous case due to the use of an old printing plate that had been left with the journal's reproduction house. As a consequence AstraZeneca had failed to comply with its undertaking. A breach of Clause 22 was ruled as acknowledged by AstraZeneca.

Taking all the circumstances into account, the Panel considered that despite AstraZeneca voluntarily bringing the matter to the attention of the Authority, the failure to ensure that the plates were destroyed constituted a breach of Clause 2 which was used as a sign of particular censure and reserved for such use. The Panel therefore ruled a breach of that clause.

Proceedings commenced 13 February 2002

Case completed 28 March 2002

CASE AUTH/1276/2/02 *NO BREACH OF THE CODE*

SERONO v FERRING

Menopur leavepiece

Serono complained about a Menopur (menotrophin) leavepiece issued by Ferring which introduced new comparative data showing that Menopur was equivalent in terms of efficacy and tolerability to Serono's product Gonal-F (follitropin alfa (rFSHa)). Both Menopur and Gonal-F were indicated to stimulate follicle development in certain amenorrhoeic women or for women undergoing superovulation within a medically assisted fertilisation programme.

The heading 'Menopur is as effective as rFSHa' was followed by the claim 'Similar pregnancy rates', beneath which was a bar chart headed 'Clinical and ongoing pregnancy rate IVF/ICSI cycle (patients completing gonadotropin administration)'. The results for clinical pregnancy were 26.6% for Menopur patients and 22.6% for follitropin alfa patients. The results for ongoing pregnancy were 23.8% for Menopur patients and 21.1% for follitropin alfa patients. Each bar was labelled with the percentage of patients.

Although the top of the page stated 'Similar pregnancy rates', Serono alleged that the bar chart, which appeared in a separate box, was misleading. The appearance of the bar chart suggested higher pregnancy rates for Menopur in both clinical pregnancy and ongoing pregnancy groups, and no statement was made about the statistical significance of the differences observed, contrary to the supplementary information to the Code which stated that 'Differences which do not reach statistical significance must not be presented in such a way as to mislead'. The bar chart for ongoing pregnancy exaggerated the differences between the groups. The percentage difference between the products for clinical pregnancy was 4% shown as a 7mm difference on the graph. The percentage difference for ongoing pregnancy was 2.7% shown as a 6mm difference on the graph. Taking into account the proportional ratio of 4% to 2.7%, the latter percentage should have been represented as a distance of 4.72mm, rather than 6mm.

The Panel noted the submission that the purpose of the leavepiece was to show comparability of Menopur with follitropin alfa. The heading to the page in question was 'Menopur is as effective as rFSHa Similar pregnancy rates'. Beneath the graph was the claim 'Similar gonadotrophin response'. The claims referred to the similarity between the products and although there were numerically higher pregnancy rates for Menopur compared to follitropin alfa, the Panel did not consider that the impression was given that this constituted a difference between the products. The Panel ruled no breach of the Code. With regard to the height of the bars, the Panel accepted the submission from Ferring that the error in the differences was 0.7mm in favour of Menopur (clinical pregnancy rate) and 0.6mm in favour of follitropin alfa (ongoing pregnancy rate). The Panel did not consider that in this instance the magnitude of the errors were such as to mean that the bar chart was visually misleading. No breach of the Code was ruled.

The claim '[Menopur is] 46.7% less expensive than recombinant FSH (follitropin alfa) per 75 IU' appeared on another part of the leavepiece beneath the claim 'At the basic NHS price, Menopur is:……' and was referenced to MIMS, March 2001. Serono stated that this comparison was based on the assumption that equal numbers of ampoules of each product were used in the treatment of patients. Such an assumption was not supported by the data on file which failed to demonstrate that equal numbers of ampoules of Menopur and r-hFSHa were utilised in the study because the findings were only given on a 'per protocol' basis rather than on an 'intention to treat' basis. The number of ampoules given to the 4–5% of patients who did not complete treatment was still a relevant consideration for prescribers. The comparison was alleged to be inaccurate. Serono was concerned about the use of the 'per protocol' population for efficacy endpoints (for example non-responders excluded). The use of a subgroup to analyse efficacy data without giving any explanation for this in the supporting evidence fell short of best standards in double blind trials, and Serono considered that it was inappropriate for this data to be used as the sole supporting reference for the leavepiece.

The Panel noted that the basic NHS cost of 10 ampoules of Menopur 75IU was £140.00 (MIMS March 2001). Follitropin alfa (Gonal-F) 75IU cost £262.50 for 10 ampoules. This was a difference of 46.7% in favour of Menopur. The supplementary information to the Code stated that price comparisons, as with any comparison, 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 summary report from the data on file stated that 36.9±10.9 ampoules of Menopur were used and that this was no different to the figures for follitropin alfa, 37±10.8 (based on the per protocol population). The Panel noted Ferring's submission that there was no difference in the number of ampoules used for each treatment between the per protocol population and the intention to treat population. The Panel did not accept that the cost comparison was inaccurate as alleged. Although the comparison appeared only to be based on the acquisition costs of each medicine the data on file had shown that there was no difference in the number of ampoules of Menopur and follitropin alfa used for similar efficacy results. No breach of the Code was ruled.

Serono Pharmaceuticals Ltd complained about a Menopur (menotrophin) leavepiece (ref E/300/03/01) issued by Ferring Pharmaceuticals Ltd. The leavepiece was to be left with a doctor after a representative had detailed the product. The leavepiece introduced new comparative data which showed that Menopur was equivalent in terms of efficacy and tolerability to Serono's product Gonal-F (follitropin alfa (rFSHa)).

Both Menopur and Gonal-F were indicated to stimulate follicle development in certain amenorrhoeic women or for women undergoing superovulation within a medically assisted fertilisation programme.

1 Page headed 'Menopur is as effective as rFSHa'

The heading was followed by the claim 'Similar pregnancy rates', beneath which was a bar chart headed 'Clinical and ongoing pregnancy rate IVF/ICSI cycle (patients completing gonadotropin administration)'. The results for clinical pregnancy were 26.6% for Menopur patients and 22.6% for follitropin alfa patients. The results for ongoing pregnancy were 23.8% for Menopur patients and 21.1% for follitropin alfa patients. Each bar was labelled with the percentage of patients. The data was referenced to Ferring – Data on File.

COMPLAINT

Serono alleged that the bar chart was in breach of Clause 7.8 in two respects. Firstly, although the top of the page stated 'Similar pregnancy rates', Serono alleged that the bar chart which appeared in a separate box, was misleading. The appearance of the bar chart suggested higher pregnancy rates for Menopur in both clinical pregnancy and ongoing pregnancy groups, and no statement was made about the statistical significance of the differences observed. Serono stated that this was contrary to the supplementary information to Clause 7.8, which stated that 'Differences which do not reach statistical significance must not be presented in such a way as to mislead'.

Secondly, the bar chart for ongoing pregnancy exaggerated the differences between the groups. The percentage difference between the products for clinical pregnancy was 4% shown as a 7mm difference on the graph. The percentage difference for ongoing pregnancy was 2.7% shown as a 6 mm difference on the graph. Taking into account the proportional ratio of 4% to 2.7%, the latter percentage should have been represented as a distance of 4.72mm, rather than 6mm.

RESPONSE

Ferring stated that the bar chart was positioned immediately below the statement, 'Similar pregnancy rates'. Nowhere had any claim been made for a superior efficacy or tolerability for Menopur over follitropin alfa – indeed, the material was entirely about the similar nature of the products. In this light, Ferring failed to understand how the bar chart, as presented could be construed as misleading.

Furthermore, the study from which this data came had now been accepted for publication in a prestigious journal after rigorous peer-review and no mention had been made to indicate that the pregnancy rates should not be considered as similar, as stated in the leavepiece.

With regard to the alleged inaccuracies in the heights of the bars, Ferring stated that the graphs were originally prepared exactly to scale using a statistical computer package. For publishing purposes they were then 'exported' to a drawing computer package. Ferring believed that the very slight change in height had occurred during this process. In its checking of the leavepiece as it returned from the printers this went unnoticed because the discrepancies were extremely small.

Ferring had examined the bar chart in detail and noted that the height of the bars should represent 2mm for each 1%; the actual heights of the bars in the clinical pregnancy rate were 52.5mm and 45.2 mm for Menopur and follitropin alfa, respectively. In theory, the heights should have been 53.2mm and 45.2mm respectively; the actual heights of the bars in the ongoing pregnancy rate were 47mm and 41mm for Menopur and follitropin alfa, respectively. In theory, the heights should have been 47.6mm and 42.2mm respectively.

From this it could be seen that Serono was correct in indicating that the gap between the bars in the ongoing pregnancy rate was very slightly too large (by 0.6mm). However, it must also be taken into account that the gap between the bars in the clinical pregnancy rate was slightly too small (by 0.7mm) and so using the ratio of the height differences to determine percentage difference in the way set out by Serono would have exaggerated the discrepancy.

Ferring supplied a comparison of the bar chart plotted accurately and as presented in the leavepiece. Ferring submitted that from this the visual differences between the graph presented in the brochure and the graph plotted accurately were negligible, and this was why it went unnoticed until now. The actual figures were prominently displayed within each of the bars. Ferring therefore did not accept that this small discrepancy had resulted in an image that could be construed as misleading.

PANEL RULING

The Panel noted the submission that the purpose of the leavepiece was to show comparability of Menopur with follitropin alfa. The heading to the page in question was 'Menopur is as effective as rFSHa Similar pregnancy rates'. Beneath the graph was the claim 'Similar gonadotrophin response'. The claims referred to the similarity between the products and although there were numerically higher pregnancy rates for Menopur compared to follitropin alfa, the Panel did not consider that the impression was given that this constituted a difference between the products. The Panel ruled no breach of Clause 7.8 of the Code.

With regard to the height of the bars, the Panel accepted the submission from Ferring that the error in the differences was 0.7mm in favour of Menopur (clinical pregnancy rate) and 0.6mm in favour of follitropin alfa (ongoing pregnancy rate). The Panel did not consider that in this instance the magnitude of the errors were such as to mean that the bar chart was visually misleading. No breach of Clause 7.8 of the Code was ruled.

2 Claim '[Menopur is] 46.7% less expensive than recombinant FSH (follitropin alfa) per 75 IU'

This appeared on another part of the leavepiece beneath the claim 'At the basic NHS price, Menopur is:……' and was referenced to MIMS, March 2001.

COMPLAINT

Serono stated that this comparison was based on the assumption that equal numbers of ampoules of each product were used in the treatment of patients. Such an assumption was not supported by the data on file which failed to demonstrate that equal numbers of ampoules of Menopur and r-hFSHa were utilised in the study because the findings were only given on a 'per protocol' basis rather than on an 'intention to treat' basis. The number of ampoules given to the 4–5% of patients who did not complete treatment was still a relevant consideration for prescribers. The comparison was alleged to be inaccurate based on the data on file, and in breach of Clause 7.2.

Serono was concerned about the use of the 'per protocol' population for efficacy endpoints (for example non-responders excluded). The use of a subgroup to analyse efficacy data without giving any explanation for this in the supporting evidence fell short of best standards in double blind trials, and Serono considered that it was inappropriate for this data to be used as the sole supporting reference for the leavepiece. Serono confirmed that this was not a separate allegation under the Code.

RESPONSE

Ferring provided a confidential extract from the statistical review of the study, which it stated clearly demonstrated that there were no statistically significant differences in the number of ampoules or vials used when either the per protocol population or the intention to treat population was employed in the analysis. This data was not to be forwarded to Serono.

The data were also presented on the basis of the per protocol population in the accepted, peer-reviewed publication. If necessary, Ferring was prepared to provide a copy of the manuscript to the Authority in confidence.

Ferring was surprised that Serono considered an analysis which comprised 94.9 and 95.7% of the total populations in each group to be a subgroup analysis and not a fair representation of the population as a whole. The available data clearly demonstrated a high degree of consistency for the results of this well controlled and important study whether analysed by either per protocol or by intention to treat populations. This fully supported the position that the efficacy of Menopur and follitropin alfa were similar and that withdrawals and cancellations were also similar for the two groups.

PANEL RULING

The Panel noted that the basic NHS cost of 10 ampoules of Menopur 75IU was £140.00 (MIMS March 2001). Follitropin alfa (Gonal-F) 75IU cost £262.50 for 10 ampoules. This was a difference of 46.7% in favour of Menopur. The claim was referenced to MIMS, March 2001. It was not referenced to the data on file. The supplementary information to Clause 7.2, price comparisons, stated that price comparisons, as with any comparison, 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 summary report from the data on file stated that 36.9±10.9 ampoules of Menopur were used and that this was no different to the figures for follitropin alfa, 37±10.8 (based on the per protocol population). The Panel noted Ferring's submission that there was no difference in the number of ampoules used for each treatment between the per protocol population and the intention to treat population. It noted Ferring's request that the data for the intention to treat population be kept confidential.

The Panel did not accept that the cost comparison was inaccurate as alleged. Although the comparison appeared only to be based on the acquisition costs of each medicine the data on file had shown that there was no difference in the number of ampoules of Menopur and follitropin alfa used for similar efficacy results. No breach of Clause 7.2 of the Code was ruled.

Complaint received **15 February 2002**

Case completed **28 March 2002**

ALLERGAN v PHARMACIA

Promotion of Xalacom

Allergan complained about a Xalacom 'Dear Doctor' letter and leavepiece issued by Pharmacia. Xalacom was an eye drop solution containing latanoprost and timolol indicated for the relief of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who were insufficiently responsive to topical beta-blockers. Pharmacia also marketed eye drops containing only latanoprost (Xalatan).

Beneath a sub-heading 'What is the rationale for Xalacom?' the 'Dear Doctor' letter stated: 'More and more patients are now benefiting from Xalatan monotherapy. But what do you do when other monotherapies prove to be insufficient and combination therapy is indicated? For these patients, and those already on fixed or loose combination, Xalacom offers a powerful source of control with convenience'. In Allergan's opinion 'a powerful source of control' constituted a reference to efficacy and hence implied that Xalacom was superior to any other monotherapy and to any other fixed or loose combination. Allergan was unaware of any data to support this. Secondly, the indication for Xalacom was 'patients … who are insufficiently responsive to topical beta-blockers'. Allergan therefore alleged it was misleading to suggest that it should be used in patients unresponsive to 'other monotherapies'.

The Panel did not consider that the claim 'a powerful source of control', implied that Xalacom was superior to any other monotherapy. In the Panel's view the claim implied that Xalacom would be an effective medicine, not that it would be more effective than anything else. Data had been supplied to support the claim. No breach of the Code was ruled.

The Panel noted that the letter referred to Xalatan monotherapy and suggested that when 'other therapies prove to be insufficient' Xalacom could be used. Although Xalacom was only indicated in patients insufficiently responsive to topical beta-blockers, this had not been stated. The letter had been sent to opthalmologists who in the Panel's view would understand that for most patients monotherapy meant beta-blockers. The Panel considered that if, in the first instance, patients had been shown to be insufficiently responsive to a topical beta-blocker, it was more likely another therapy would be added in rather than the monotherapy changed altogether. On balance, given the intended audience and the Stepwise way in which glaucoma was treated, the Panel did not consider that the letter was misleading by suggesting that Xalacom could be used when monotherapies other than Xalatan had proved insufficient and combination therapy was indicated. No breach of the Code was ruled.

Allergan alleged that the phrase in the leavepiece 'When monotherapy is insufficient …' was misleading. The phrase appeared under the headline 'Powerful IOP control with once a day convenience' which constituted a reference to efficacy and in Allergan's view implied that Xalacom was superior to any other monotherapy, without any known supporting evidence. The indication for Xalacom was 'patients … who are insufficiently responsive to topical beta-blockers'. Allergan therefore alleged that it was misleading to suggest that it should be used in patients unresponsive to other monotherapies.

The Panel noted its comments made upon the 'Dear Doctor' letter above. The Panel did not consider that the claims now at issue implied that Xalacom was superior to any other monotherapy as alleged and no breach of the Code was ruled.

With regard to the patient population for whom Xalacom was indicated the Panel again referred to its comments on the 'Dear Doctor' letter above and ruled no breach of the Code.

Allergan Ltd complained about a Xalacom 'Dear Doctor' letter (ref P6607/8/01 391-0011) and leavepiece (re P6607/8/01 391-0011) issued by Pharmacia Limited. Xalacom was an eye drop solution containing latanoprost and timolol indicated for the relief of intraocular pressure (IOP) in patients with open angle glaucoma and ocular hypertension who were insufficiently responsive to topical beta-blockers. Pharmacia also marketed eye drops containing only latanoprost (Xalatan).

A 'Dear Doctor' letter

Beneath a sub-heading 'What is the rationale for Xalacom?' the 'Dear Doctor' letter stated:

'More and more patients are now benefiting from Xalatan monotherapy. But what do you do when **other** monotherapies prove to be insufficient and combination therapy is indicated?

For these patients, and those already on fixed or loose combination, Xalacom offers a powerful source of control with convenience.'

COMPLAINT

Allergan quoted the two paragraphs at issue although it misquoted the first sentence replacing Xalatan with Xalacom to read 'More and more patients are now benefiting from Xalacom monotherapy'

Allergan alleged that the two paragraphs were misleading in breach of Clause 7.2 for two reasons. Firstly, although the second sentence specifically mentioned convenience, the phrase 'a powerful source of control' referred to efficacy. In Allergan's opinion this implied that Xalacom was superior to any other monotherapy and to any other fixed or loose combination; it was unaware of any date to support this.

Secondly, the Xalacom summary of product characteristics (SPC) stated the indication as 'patients … who are insufficiently responsive to topical beta-blockers'. Allergan therefore considered that it was misleading to suggest that it should be used in patients unresponsive to other monotherapies.

RESPONSE

Pharmacia emphasized some points which appeared

to be potentially confusing: Xalacom was not monotherapy, it was a fixed dose combination therapy comprising latanoprost 0.005% and timolol 0.5% in a single drop; latanoprost 0.005% was marketed as Xalatan by Pharmacia and licensed as a monotherapy; monotherapy was typically the first step in the medical treatment of glaucoma and due to the progressive nature of the disease monotherapy was frequently followed by combination therapy, which might be given in fixed or loose combination.

Turning to the complaint itself Pharmacia noted that Allergan had misquoted the letter by referring to Xalacom in the first sentence at issue instead of Xalatan. Pharmacia stated that the claim 'more and more patients are now benefiting from Xalatan monotherapy' was a fact borne out by DIN-Link figures.

Pharmacia refuted the allegation that the phrase 'a powerful source of control with convenience' implied that Xalacom was superior to any other therapy. 'Powerful' was not a superlative. Pharmacia provided copies of advertisements issued by a number of different pharmaceutical companies in which the word 'powerful' had been used.

Pharmacia stated that proof of efficacy of Xalacom had been provided in two pivotal studies which had been referred to in the 'Dear Doctor' letter (Higginbotham *et al*, data on file, Pfeiffer *et al*, data on file). Pharmacia submitted that the phrase was not in breach of Clause 7.2 of the Code. Studies showing superior efficacy of Xalatan over timolol, brimonidine and dorzolamide were provided (data on file 1996, Kampik *et al*, O'Donoghue *et al* 2000). Although those studies did not directly compare Xalacom with the mentioned products, they were comparative trials using one of the two components of Xalacom.

Pharmacia submitted that Allergan's second point, that it was misleading to suggest that [Xalacom] should be used in patients unresponsive to other monotherapies, was pedantic, especially in light of the fact that Allergan raised an almost identical issue against another company in 1999, Case AUTH/831/1/99. No breach of the Code was ruled.

Pharmacia stated that it was true that Xalacom was indicated in patients unresponsive to topical beta-blockers. As was shown in the European Glaucoma Society Guidelines, topical beta-blockers were considered to be standard monotherapy, with other medicines added in either as replacement or in combination. This could reasonably be assumed as common knowledge within the target audience of the letter. Hence, it was reasonable to make the above statement regarding the use of Xalacom in these patients. A copy of the European Guidelines was provided.

PANEL RULING

The Panel noted that Allergan had misquoted the letter – replacing one product name with another. The Panel made its ruling based on what the letter actually stated.

The Panel did not consider that the claim 'a powerful source of control', implied that Xalacom was superior to any other monotherapy and to any other fixed or loose combination as alleged. In the Panel's view the claim implied that Xalacom would be an effective medicine, not that it would be more effective than anything else. Studies had been submitted showing that Xalacom provided significantly greater IOP reductions than either of its constituent monotherapies, latanoprost and timolol (Higginbotham *et al*, Pfeiffer *et al*). No breach of Clause 7.2 was ruled.

The Panel noted that glaucoma was commonly first treated with a topical beta-blocker unless such medicines were contra-indicated or patients were intolerant of them. The British National Formulary (BNF) (No 42, September 2001) stated that other medicines could be added as necessary to control intraocular pressure. The Panel noted that the letter referred to Xalatan monotherapy and suggested that when 'other monotherapies prove to be insufficient' Xalacom could be used. Although Xalacom was only indicated in patients insufficiently responsive to topical beta-blockers, this had not been stated. The letter was, however, sent to ophthalmologists who, in the Panel's view, would understand that for most patients monotherapy meant beta-blockers. For those patients for whom monotherapy with a beta-blocker was insufficient another medicine could be added or the patient could be given Xalacom. For those patients for whom monotherapy was not a beta-blocker, Xalacom would probably be contra-indicated by virtue of its timolol content ie because such patients had already been shown to be contra-indicated or intolerant to beta-blocker therapy. The Panel considered that if, in the first instance, patients had been shown to be insufficiently responsive to a topical beta-blocker, it was more likely that as recommended in the BNF, another therapy would be added in rather than the monotherapy changed altogether. On balance, given the intended audience and the stepwise way in which glaucoma was treated, the Panel did not consider that the letter was misleading by suggesting that Xalacom could be used when monotherapies other than Xalatan had proved insufficient and combination therapy was indicated. No breach of Clause 7.2 was ruled.

B Leavepiece

The design of the leavepiece was such that by pulling either end of a flap encased in an outer cover, two 'pages' emerged above and below the cover. The top pull-out page featured the claim 'When a monotherapy is insufficient and convenience is a factor'. Below the claim were four bullet points under the heading 'New Xalacom for control'. The second bullet point read 'Greater efficacy than monotherapy with either Xalatan or timolol'.

COMPLAINT

Allergan alleged that the phrase 'When monotherapy is insufficient' was misleading, in breach of Clause 7.2 of the Code for the same reasons as stated in point A above. The phrase appeared under the headline 'Powerful IOP control with once a day convenience' which constituted a reference to efficacy. In Allergan's

view this implied that Xalacom was superior to any other monotherapy and it was unaware of any data to support this. One of the lower bullet points stated 'Greater efficacy than monotherapy with either Xalacom or timolol' but this could not be considered sufficient qualification of the more prominent statement above.

The Xalacom SPC stated the indication as 'patients … who are insufficiently responsive to topical beta-blockers'. Allergan therefore considered that it was misleading to suggest that it should be used in patients unresponsive to other monotherapies.

RESPONSE

Pharmacia rejected the allegation that the claim 'Powerful IOP control with once a day convenience' implied superiority to any other monotherapy for the same reasons as stated in point A above.

Pharmacia also refuted Allergan's second point, that it was misleading to suggest that [Xalacom] should be used in patients unresponsive to other monotherapies as the indication for Xalacom was in patients who were insufficiently responsive to topical beta-blockers, for the same reasons as set out in point A above.

PANEL RULING

The Panel noted that Allergan had again misquoted one of the claims and replaced Xalatan with Xalacom when referring to 'Greater efficacy than monotherapy with either Xalacom or timolol'. The claim on the leavepiece actually referred to Xalatan and it was on the basis of that claim that the Panel made it ruling.

The Panel noted its comments made in point A above. The Panel did not consider that the claims now at issue implied that Xalacom was superior to any other monotherapy as alleged. No breach of Clause 7.2 was ruled.

With regard to the patient population for whom Xalacom was indicated the Panel referred to its comments in point A above and again ruled no breach of Clause 7.2 of the Code.

During its consideration of this case the Panel was concerned that the reference numbers of both the 'Dear Doctor' letter and the leavepiece were identical; P6607/8/01 391-0011. In each instance the reference number appeared below the Pharmacia Ophthalmology logo. A second reference number (P6574/7/01) appeared on both pieces at the end of the Xalacom prescribing information. Point 1 of the Guidelines on Company Procedures Relating to the Code of Practice (page 40 of the Code of Practice booklet) referred to certification of promotional material. It was stated that a particular reference number should relate to only one item of promotional material. The Panel requested that Pharmacia should be advised of its concerns in this regard.

Complaint received **15 February 2002**

Case completed **4 April 2002**

CASE AUTH/1278/2/02

PRIMARY CARE GROUP PHARMACEUTICAL ADVISER v TRINITY

Conduct of representative

A pharmaceutical adviser to a local primary care group (PCG), complained about the activities of the local project coordinator for Trinity.

The complainant was contacted by a practice which was querying the project coordinator's activities; she had given the practice the impression that she was working with the PCG on prescribing budgets, asking if the PCG was happy for her to obtain information about prescribing.

Prior to this query, the complainant had never heard of the project coordinator nor worked with her or her company. The complainant checked with all her colleagues in the PCG and no-one was working, or had ever worked, with her or anyone from Trinity. Trinity's regional business manager suggested the project coordinator had not told the complainant's practice she was working with it specifically but with other local PCGs. Even if this was so, the impression left was different, and therefore the information presented was misleading.

The complainant had asked Trinity which other primary care organisations (PCOs) it was involved with, the response was that it was currently working with two other PCGs. The complainant contacted the pharmaceutical advisers of both organizations and they replied they were not working with the project coordinator or Trinity.

The complainant alleged that the behaviour of the project coordinator was totally inappropriate; she could only assume that Trinity was trying to access prescribing data in a most underhand fashion.

Documentation submitted by Trinity showed that in some cases PCG personnel had met with Trinity or were working with the company on an individual practice basis. The Panel considered that to state or imply that an activity was endorsed by or otherwise formed part of official PCG policy would carry great weight with practices within the PCG. There was an important difference between an activity being official PCG policy and a company either holding meetings to discuss activities with the PCG or PCG personnel playing a role in such activities at the request of a GP practice. The fact that a PCG did not object to an activity did not mean that it was PCG policy, it was important in such situations to be entirely clear. Trinity had met PCG personnel to discuss a switch programme and subsequently, at the practices' request, PCG personnel had become involved. Nonetheless the complainant and practices within her PCG had gained the impression that Trinity and PCGs were officially working together on the Trinity switch programme and insofar as this implied that the switch programme had been officially endorsed by the PCG that was not so. Trinity had not been sufficiently clear about the role of the PCG. High standards had not been maintained; a breach of the Code was ruled.

A pharmaceutical adviser, for a local primary care group (PCG), complained about the activities of the local project coordinator for Trinity Pharmaceuticals Ltd.

COMPLAINT

The complainant was contacted by a practice which was querying the local project coordinator's activities; she had given the practice the impression that she was working with the PCG on prescribing budgets, asking if the PCG was happy for her to obtain information about prescribing.

Prior to this query, the complainant had never heard of the local project coordinator and certainly did not work, nor had ever worked, with her or her company. The complainant checked with all her colleagues in the PCG and no-one was working, or had ever worked, with her or anyone from Trinity. The complainant then contacted the company and spoke with the regional business manager, who suggested the local project coordinator had not told the complainant's practice that she was working with it specifically but with other local PCGs. Even if this was so, the impression left with the practice was different and therefore the way her information was presented was misleading.

The complainant had asked the regional business manager which other primary care organisations (PCOs) Trinity was involved with and his unequivocal response was that his company was undertaking joint working with two other local PCGs at present. The complainant contacted the pharmaceutical advisers of both organizations and their replies were equally unequivocal; they were not working with the local project co-ordinator or Trinity. These replies were provided.

The complainant therefore contacted neighbouring pharmaceutical advisers and again received replies that they too had had complaints about the activities of Trinity in two other areas.

The complainant alleged that the behaviour was totally inappropriate and could only assume Trinity was trying to access prescribing data in a most underhand fashion. On behalf of the PCO pharmaceutical advisers in this area, the complainant was therefore writing to complain in the strongest terms.

When writing to Trinity the Authority drew attention to Clauses 2, 7.2, 9.1 and 15.2 of the Code.

RESPONSE

Trinity stated that the regional business manager was asked to telephone the complainant on 6 February as she was concerned that (according to a member of practice staff who remained unidentified) the local project coordinator had been informing some surgeries that she was actively working with the complainant's PCG.

The regional business manager telephoned and informed the complainant that although Trinity was working with many PCGs in a local area, giving three examples, the local project coordinator had not mentioned the complainant's PCG as the company had not yet had any meetings with that particular PCG. The regional business manager explained that what had most likely happened was that the member of practice staff misinterpreted what was said by the local project coordinator. The complainant then went on to warn the regional business manager that unless she received a written explanation of the situation then she would complain to the ABPI. A written explanation was immediately sent on 8 February. In any event, the complainant considered it necessary to formally complain. The complainant stated that she had checked with her colleagues at other PCGs and that they stated that they were not working with, nor had they ever worked with the local project co-ordinator. In fact Trinity had worked successfully with these PCGs and as evidence of this provided a copy of an email from the previous prescribing support pharmacist for a local health authority who worked for a local PCG; a supportive letter sent by the prescribing support pharmacist for the another local PCG; and a letter to Unichem from the prescribing support pharmacist for a local PCG underlining the support within the local PCGs for a Trinity branded product. In addition if required a full diary of contacts made with PCGs within the area would be supplied.

Trinity stated that one element of the misunderstanding might be due to the turnover of staff at PCGs. It would however forward some names of key PCG individuals who would be happy to be contacted in order to verify that Trinity was in actual fact working with them during recent months.

Having interviewed the project coordinator, Trinity assured the Authority that there had been absolutely no attempt to mislead practices/PCGs in any way. The local project coordinator met the definition set out in Clause 1.6 of the Code in that she called on members of the health professions and administrative staff in relation to the promotion of medicines. She had passed her ABPI representatives examination and had always behaved extremely professionally in all areas of her work.

In summary, Trinity stated that the project coordinator had fully complied with the Code in all areas of contact with health professionals and had met all requirements of Clauses 2, 7.2, 9.1 and 15.2 of the Code.

* * * * *

With the agreement of Trinity its response was sent to the complainant for further comment.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant noted that the complaint originated from the fact that one of the practices in the PCG had been given the impression by the local project coordinator that Trinity was working with the PCG. If what the local project coordinator actually said was that she was working with 'local PCGs', nevertheless the impression she gave to this practice was that this included the local PCG, which was clearly misleading.

The complainant had received an apology from the regional business manager and having spoken with him she was prepared to accept that it was only this one representative who had given a misleading picture. However, the complainant subsequently learnt from another local pharmaceutical adviser that this approach was occurring in other areas and therefore considered the apology was not sincere and with the support of other local advisers submitted the complaint.

With regard to Trinity 'working with other local PCGs' the complainant noted that the company did not put forward evidence that it was working with a particular local PCG, as was alleged by the regional business manager. In addition if a diary of contacts made with PCGs constituted 'working with PCGs' this would be totally disingenuous.

The complainant noted that Trinity appeared to consider that copies of correspondence from local PCGs provided evidence of the company successfully working with these PCGs. In fact, there was no evidence for this. The email from the previous prescribing support pharmacist for a local health authority stressed that the work which was undertaken in the two practices was undertaken on the initiative of the practices and 'this was not a PCG project'. Trinity's letter dated 4 March stated that the letter sent by a doctor to a representative underlined that the representative was working with a local PCG. However the letter clearly stated that it was the practice which decided to work with Trinity, and it was not a PCG policy. The complainant quoted 'There was no suggestion that the local PCG was advocating any particular company and the decision as to whether to proceed was purely a practice one'.

The doctor also stressed that the involvement of a previous local health authority prescribing support pharmacist was not a PCG sanction but purely to give him 'experience in an area that was likely to become increasingly important for pharmacy advisers'.

Neither of the current prescribing support pharmacist's letters stated at any point that the PCG was working with Trinity. She stated 'I recently met with some representatives from Trinity'. The complainant stressed that meeting a representative could not constitute 'working with the company'. When advisers recommended a product or package they did so having looked into the merits based on available evidence and information. This did not give the company the right to imply it was 'working with the PCG'. In fact such a practice would undermine such recommendations if it could be viewed that the adviser was biased. The current prescribing support pharmacist's second letter was purely to ensure continuity of supply of one particular product. Any adviser might do the same for any product which appeared to be in short supply.

Clearly, for Trinity to make the leap to this constituting 'working with the PCG' was both disingenuous and unacceptable practice. A visit by a representative to one GP practice in an area deciding

on a medicine switch, did not constitute working with the whole primary care organisation.

The complainant noted that Trinity had offered to forward names of key PCG individuals who would be happy to be contacted in order to verify that the company was working with them in recent months. Depending on one's definition of 'recent': the current pharmaceutical adviser for local PCGs had confirmed they were not working with Trinity; the previous prescribing support pharmacist for a local PCG stated in his e-mail that the PCG was not involved with Trinity; the local PCG prescribing lead stressed the PCG was not working with Trinity; the local PCG prescribing support pharmacist did not state that the PCG had been working with Trinity.

The complainant stated that Trinity clearly did not appreciate that if the PCGs had worked with the company, as implied, and the PCG promoted the company's products, the PCGs could have been acting illegally with respect to the Medicines (Advertising) Regulations 1994 and could have been in breach of HSC (93)5 'Standards of Business Conduct for NHS staff'.

In summary, none of Trinity's enclosures supported the company's claim that it was working with local PCGs. Trinity had not substantiated the claim by the regional business manager that the company was working with a local PCG. Whatever the local project co-ordinator said to the GP practice, the impression given was that she was working with the local PCG. This approach was being adopted elsewhere.

The complainant hoped that her complaint had highlighted the need for pharmaceutical company representatives not to choose to give misleading and damaging impressions of their involvement with PCOs.

PANEL RULING

The Panel noted that the complainant was concerned that a practice within the local PCG had gained the impression from a representative that the PCG was working jointly with Trinity. The company stated that this was not so but stated that it was working with many PCGs in the local area as examples. The complainant stated that she was also advised by the company that it was working with another local PCG.

The Panel considered Trinity's submission. The previous prescribing support pharmacist at a local PCG described his role in relation to switches to Trinity slow-release products by two practices within the PCG stating that both projects were initiated after contact by Trinity with the practices concerned; they were not PCG projects. A letter dated 21 May 2001 from a prescribing support pharmacist at a local PCG to a GP practice highlighted potential savings of a switch package to Trinity's sustained release products. For further details the GP was invited to contact the prescribing support pharmacist or Trinity to arrange to see the representative. A further letter dated 25 February 2002 from a GP practice (and a local PCG prescribing lead) which had effected a switch confirmed that the local PCG was not advocating any particular company and the decision to proceed was a practice one. The complainant had submitted evidence from the present prescribing team manager at local PCGs that, *inter alia*, the PCGs were not currently working with Trinity nor had they had discussions in meetings with Trinity about joint working.

The Panel considered that to state or imply that an activity was endorsed by or otherwise formed part of official PCG policy would carry great weight with practices within the PCG. There was an important difference between an activity being official PCG policy and a company either holding meetings to discuss activities with the PCG or PCG personnel playing a role in such activities at the request of a GP practice. The fact that a PCG did not object to an activity did not mean that it was PCG policy. It was important in such situations to be entirely clear about the extent of the PCG's role and its approval of the activity in question. It was clear that Trinity had met PCG personnel prior to May 2001 to discuss the switch programme and that subsequently, at the practices' request, PCG personnel had become involved. Nonetheless the complainant and practices within her PCG had gained the impression that Trinity and PCGs were officially working together on the Trinity switch programme and insofar as this implied that the switch programme had been officially endorsed by the PCG that was not so. Trinity had not been sufficiently clear about the role of the PCG. High standards had not been maintained; a breach of Clause 9.1 was ruled.

The Panel did not consider that the circumstances warranted a ruling of breaches of Clauses 2, 7.2 and 15.2 of the Code; no breach of these clauses was ruled.

Complaint received **15 February 2002**

Case completed **1 May 2002**

HEALTH AUTHORITY MEDICAL ADVISER v GLAXOSMITHKLINE

Conduct of representative

A medical adviser to a health authority complained that a representative from GlaxoSmithKline was giving misleading instructions to nurses with regard to new evidence on the needle lengths to be used for administering vaccines. The representative was supplying copies of the 'UK Guidance on Best Practice in Vaccine Administration' which the health authority was happy with but was making inappropriate claims about poor practice if nurses did not switch to ordering GlaxoSmithKline vaccines which were supplied with a choice of needle lengths.

Unfortunately, the practices that had complained to the health authority were unwilling to become involved in a formal complaint.

The representative was also reported to claim that the manager of a local education board was supporting her approach and specifically approved needle lengths. The manager had made it clear that she did not endorse any meetings organised by representatives.

The Panel noted that the parties' accounts of what took place differed. It was difficult to know exactly what had transpired between the parties. The Panel was concerned that the nurses considered that they had been intimidated by the representative's presentation which had discussed needle length.

The Panel noted that it had previously considered a complaint about the booklet 'UK Guidance on Best Practice in Vaccine Administration', Case AUTH/1258/11/01. No breach of the Code had been ruled.

The guidance referred to 'Choice of needle' and stated that 'The correct length and gauge of the needle are key in ensuring that the vaccine is delivered to the correct location as painlessly as possible and with maximum immunogenicity'. The shortest needle recommended in any patient group was 25mm which the Panel noted was consistent with WHO Guidance on immunizaton. Readers were told that if they considered that the needle length would not be sufficient to deliver the vaccine to the appropriate site then an alternative should be sought. It was not stated that some vaccines were supplied with a fixed 16mm needle and others with a fixed 25mm needle. Readers were told however that those vaccines supplied with non-fixed needles allowed individual choice on needle length.

Turning to the case now before it, Case AUTH/1279/2/02, the Panel considered that given the parties' differing accounts, and the reluctance of the practices to provide further information, it was not in a position to determine what had happened, although it was concerned about the alleged conduct of the representative, particularly given the previous case about the booklet (Case AUTH/1258/11/01). It considered however that there was insufficient evidence in the present case and therefore ruled no breach of the Code.

A medical adviser to a health authority complained about the conduct of a representative from GlaxoSmithKline.

COMPLAINT

The complainant alleged that the representative was giving misleading instructions to nurses in the area. She was using new evidence on needle lengths that had raised concerns amongst staff regarding their previous practice.

The representative was supplying copies of the booklet 'UK Guidance on Best Practice in Vaccine Administration' which the health authority was happy with but was making inappropriate claims about poor practice if nurses did not switch to ordering GlaxoSmithKline vaccines which were supplied with a choice of needle lengths.

Unfortunately, the practices that had complained to the health authority were unwilling to become involved in a formal complaint. However, a local PCG Clinical Governance Group was of the opinion that it should be reported to the Authority.

The representative was also reported to claim that the manager of a local education board was supporting her approach and specifically approved needle lengths. The manager had made it clear that she did not endorse any meetings organised by representatives.

RESPONSE

GlaxoSmithKline stated that it had sponsored the book 'UK Guidance on Best Practice in Vaccine Administration' by means of an educational grant. The representative had conducted a series of meetings with practice nurses in the area to discuss the general scope, content and the background of the guidance and that had led to discussion about the individual sections of the guidance including needle length.

When questioned by the practice nurses about vaccines in the market and the needle length section, the representative highlighted that some GlaxoSmithKline vaccines complied with the guidance. For those vaccines that currently did not comply with the guidance, GlaxoSmithKline was working to update the presentations to be in line with best clinical practice. The representative did not criticise at any time any other companies' products and had only discussed GlaxoSmithKline vaccines when questioned in relation to best practice and the needle length section of the guidance.

The representative denied making any claims to practice nurses of poor practice if they were using fixed needle vaccines.

Whilst talking to practice nurses about the guidance, her intention was not to offend them but to promote best clinical practice that was evidence based.

The representative had acted according to the briefing relating to the use of the guidance. In her customer interactions, she had talked about the document as an entity.

The representative had a good working relationship with the manager of the local education board who was aware that she was conducting meetings in the area to discuss the guidance. The manager provided address labels of the practice nurses in the local area and requested the names of those attending these meetings so that she could have a record of their meetings and training attendance. At no time had the representative claimed that the manager supported her alleged approach regarding promotion of needle choice or endorsed any of her meetings. The GlaxoSmithKline Vaccines representatives were all briefed via a telephone conference by their area sales managers following the outline below:

- Background about the guidance development with the setting up of the Vaccine Administration Taskforce.
- Who was involved in the development of this guidance ie the Vaccine Administration Taskforce members.
- Why the guidance development was initiated – following the NOP survey in 500 practice nurses and other additional feedback from practice nurses about the need for guidance on vaccine administration.
- How the guidance was an independent source that had been endorsed by a number of independent and highly respected organisations.
- The scope of GlaxoSmithKline's involvement in sponsoring the initiative and payment of printing and the involvement of Shire Hall Communications.
- How copies could be ordered from GlaxoSmithKline's distribution centre or directly from Shire Hall Communications.
- How the guidance should be used;
    - It was emphasised that the guidance was a valuable source and that its independence should be treated with respect.
    - The guidance should be used to promote best clinical practice in vaccine administration and should not be used to disparage any current or past clinical practice or products.
- There was no charge for copies of the guidance.
- There were limited copies and requests for reprints could be made to Shire Hall Communications.
- The GlaxoSmithKline Vaccines representatives could discuss this item and had access to copies of this item.
- There was important information regarding vaccination, from taking vaccines out of the fridge to the disposal of the vaccine; and chapters of the guidance included information about the cold chain, reconstitution of vaccines and needles etc.

The representatives were then updated on GlaxoSmithKline's strategy of moving towards non-fixed presentations and needle length in order to be compliant with the guidance. Finally, it was re-emphasised that this guidance should be used to promote best clinical practice for vaccine administration and should not be used in any way to disparage the products on the market previously or presently by other companies or GlaxoSmithKline.

In addition to the verbal briefing, an email was sent to the representatives in December 2001 which set out the actions that GlaxoSmithKline proposed to comply with best clinical practice within the vaccine portfolio.

GlaxoSmithKline had recently emailed its representatives to reiterate the original briefing the company gave them about the use of the guidance. A copy of this email was provided.

To discuss needle length with customers, a series of peer reviewed medical journal articles had been used by the representatives. (Zuckerman 2000, Diggle and Deeks 2000 and Poland *et al* 1997). A visual aid of a fat pad had been used to illustrate the necessity of true intramuscular administration of vaccines. This issue had also been illustrated with MRI (magnetic resonance imaging) scans of injections into the subcutaneous tissue and the muscle mass following injections in the deltoid region with needles of varying lengths. Copies of these items were provided.

FURTHER COMMENTS FROM THE COMPLAINANT

GlaxoSmithKline's response was sent to the complainant for comment prior to the Panel making a ruling.

The complainant stated that GlaxoSmithKline stressed that it taught the representatives to emphasise 'best practice' but it was the emphasis on this that had bullied nurses into believing that they were failing their patients if they did not use GlaxoSmithKline vaccines.

Unfortunately the situation was that there was the representative's statement that she did not accuse anyone of poor practice in the two practices which stated she was intimidating nurses by her presentation. The practices that brought the complaint did not want to proceed as they had a good relationship with the representative despite the concerns raised.

The complainant stated that on reflection, after reading the company instructions, this was an example of a representative who had been over zealous in presenting information in a biased way – as the complainant's understanding was that needle length was still being debated and not agreed by all. It might be useful to feed back to the company that the representative's demonstration with a sponge to signify needle deposition left the nurses feeling that for years they had been causing harm to patients. Visual images were very powerful but in this instance led to raised anxiety.

PANEL RULING

The Panel noted that the parties' accounts of what took place differed. The Panel observed that it was

difficult in such cases to know exactly what had transpired between the parties. A judgement had to be made on the evidence which was available, bearing in mind that extreme dissatisfaction was usually necessary for a complaint to be made.

The Panel was concerned that the nurses considered that they had been intimidated by the representative's presentation which had discussed needle length.

The Panel noted that it had previously considered a complaint about the booklet 'UK Guidance on Best Practice in Vaccine Administration', Case AUTH/1258/11/01. No breach of the Code had been ruled. In that case GlaxoSmithKline had stated that its representatives had been given a copy to use with customers. Representatives were verbally briefed and asked to respect the independence of the guidance when discussing its contents with customers. No written briefing material was given.

In Case AUTH/1258/11/01 the Panel had noted that pages 39-41 of the guidance referred to 'Choice of needle'. The first sentence in this section stated that 'The correct length and gauge of the needle are key in ensuring that the vaccine is delivered to the correct location as painlessly as possible and with maximum immunogenicity'. Readers were further informed that for an intramuscular injection the needle length should be 25mm. In a highlighted box of text entitled 'Recommended Choice of Needle Lengths' the shortest needle recommended in any patient group was 25mm. It was also suggested that a 25mm needle should be used if an injection was to be given subcutaneously. The Panel noted that the WHO in its document relating to global vaccines and immunization 'Module 4 Ensuring safe injections' recommended a 25mm needle length for all intramuscular or subcutaneous injections.

The Panel noted that the section of the booklet in question did not refer to any specific vaccines. General advice regarding needle length was given which was consistent with WHO recommendations. Readers were not told that some vaccines were supplied with a fixed 16mm needle. The Panel noted that the fact that vaccines with 16mm fixed needles were licensed might be seen as a recommendation for that needle length. The section was positive for a 25mm needle length.

The Panel noted that nowhere in the booklet was any specific vaccine mentioned. The section on choice of needle recommended a 25mm needle for most patient groups and injection routes. A chapter in the booklet entitled 'Technique' discussed prefilled syringes and ampoules. Readers were told that if they considered that the needle length would not be sufficient to deliver the vaccine to the appropriate site (ie due to a thick layer of fat for IM injection) then an alternative should be sought. It was not stated that some vaccines were supplied with a fixed 16mm needle and others with a fixed 25mm needle. Readers were told however that those vaccines supplied with non-fixed needles or in ampoules, allowed individual choice on needle length.

Turning to the case now before it, Case AUTH/1279/2/02, the Panel was concerned that the representative had organised meetings specifically to discuss the guidance; this appeared to be slightly at odds with GlaxoSmithKline's response to the previous case which referred more generally to discussing the content with customers. In addition, a series of peer reviewed articles had been used by the representatives to discuss needle length with customers (Zuckerman, Diggle and Deeks and Poland *et al*) all of which advocated the use of a 25mm needle in the majority of patients. The Panel considered that GlaxoSmithKline would be well advised to have good written briefing material about what the representatives could and could not say about the guidance. In its view the telephone briefing and the emails were insufficient as there appeared to be no written instructions on how to use, discuss and present the content of the guidance. GlaxoSmithKline must ensure that vaccines with fixed needles of length other than 25mm were not disparaged by GlaxoSmithKline's use of the booklet; vaccines with 16mm fixed needles were licensed in the UK.

Given the parties' differing accounts of the meetings and the reluctance of the practices to provide further information or comment the Panel was not in a position to determine what precisely had happened. The Panel was concerned about the alleged conduct of the representative particularly given the previous case. It considered however that there was insufficient evidence and therefore ruled no breach of Clauses 15.2 and 15.4 of the Code.

Complaint received **15 February 2002**

Case completed **17 May 2002**

CASE AUTH/1280/2/02

NOVA NORDISK V SOLVAY HEALTHCARE

Femoston-conti leavepiece

Novo Nordisk complained about a leavepiece for Femoston-conti (oestradiol 1mg and dydrogesterone 5mg) issued by Solvay Healthcare. Novo Nordisk marketed another continuous combined hormone replacement therapy (HRT) preparation, Kliovance (oestradiol 1mg and norethisterone 0.5mg). Under a heading of 'Lipid profile enhancement' appeared two claims 'Dydrogesterone maintains the positive effect of oestrogen on HDL-cholesterol' (Whitehead 1994), and 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance' (Samsioe *et al* 1998). A graph depicted the total cholesterol and HDL-cholesterol changes from baseline after 12 months' treatment with Femoston-conti; –6.4% and +7.4% respectively.

Novo Nordisk noted that the Femoston-conti induced rise in triglycerides found in a Solvay Healthcare study was not mentioned and considered this omission was potentially misleading, particularly under the heading 'Lipid profile enhancement'.

The Panel noted that the Femoston-conti summary of product characteristics (SPC) stated 'Triglyceride levels were raised overall but usually remained within the normal range'. The corresponding Kliovance SPC stated 'Kliovance did not increase triglycerides levels'. The Panel did not consider that omission of the triglyceride data was misleading and no breach of the Code was ruled in that regard.

Novo Nordisk alleged that it was misleading to compare dydrogesterone with Kliovance, rather than comparing dydrogesterone with norethisterone acetate, and that this had been done in an unbalanced way. The Panel did not consider it was misleading *per se* to compare dydrogesterone with Kliovance and no breach of the Code was ruled.

Novo Nordisk alleged that the claim 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance' strongly implied a negative effect on the lipid profile in comparison to dydrogesterone. In fact HDL-cholesterol did tend to decrease over 12 months, but this decrease was not statistically different from placebo. The Samsioe abstract stated that, 'Although HDL-cholesterol tended to decrease… the LDL/HDL ratio did not change', and concluded that, because LDL-cholesterol decreased, 'favourable changes in lipid and lipoprotein parameters were seen' with Kliovance. Novo Nordisk considered that a typical recipient of the leavepiece would be left under the misleading impression that Kliovance had a negative effect on the lipid profile, whereas in fact the effect of Kliovance on the lipid profile was positive or, at worst, neutral, hence this was a misleading comparison.

The Panel considered that the claim 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance' implied that Kliovance had a negative effect on the plasma lipid profile. The claim was referenced to an abstract (Samsioe *et al*) which also noted that the LDL/HDL-cholesterol ratio did not change and concluded that favourable changes in lipids and lipoproteins were seen with Kliovance. The Panel noted that similarly the Kliovance SPC also referred to a decrease in HDL-cholesterol over time without any change in the LDL/HDL ratio. The Panel considered that the claim in question did not reflect the whole of the data with regard to the effect of Kliovance on HDL-cholesterol and so was misleading in that regard. A breach of the Code was ruled.

Upon appeal of this ruling, the Appeal Board considered that the claims 'Dydrogesterone maintains the positive effect of oestrogen on HDL-cholesterol' and 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance', taken together, implied that Femoston-conti had a positive effect on plasma lipids and that Kliovance had a negative effect. The claim 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance' did not reflect the whole of the data and thus gave a misleading impression. This was further compounded by the heading 'Lipid profile enhancement'. The claims were limited to the effects of each treatment on HDL-cholesterol whereas the lipid profile was composed of many other lipid fractions. The Appeal Board considered that the claim was misleading and upheld the Panel's ruling of a breach of the Code.

Novo Nordisk Limited complained about a leavepiece (ref FEM216) for Femoston-conti (oestradiol 1mg and dydrogesterone 5mg) issued by Solvay Healthcare Limited. Novo Nordisk marketed another continuous combined hormone replacement therapy (HRT) preparation, Kliovance; Kliovance also contained oestradiol 1mg but the progestogen component was provided in the form of norethisterone 0.5mg. Under a heading of 'Lipid profile enhancement' appeared two claims 'Dydrogesterone maintains the positive effect of oestrogen on HDL-cholesterol', referenced to Whitehead (1994), and 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance' referenced to Samsioe *et al* (1998). A graph to the right of the claims depicted the total cholesterol and HDL-cholesterol changes from baseline after 12 months' treatment with Femoston-conti; –6.4% and +7.4% respectively. This data was referenced to Solvay Healthcare, H102.5011.02.

COMPLAINT

Novo Nordisk accepted that the presented data (ref. Solvay Healthcare) showed that Femoston-conti modestly lowered LDL and total cholesterol and modestly increased HDL-cholesterol and that this was a positive effect overall. However the rise in triglycerides found in the study was not mentioned on the leavepiece and Novo Nordisk considered that this was potentially misleading by omission of important and relevant information, particularly under the heading 'Lipid profile enhancement'.

In the same section of the leavepiece it was stated that 'HDL-cholesterol tended to decrease after 12 months

treatment with Kliovance', strongly implying a negative effect on the lipid profile in comparison to dydrogesterone. In fact HDL-cholesterol did tend to decrease over 12 months, but this decrease was not statistically different from placebo. The Samsioe abstract to which the claim was referenced stated that 'Although HDL-cholesterol tended to decrease… the LDL/HDL ratio did not change', and concluded that, because LDL-cholesterol decreased, 'favourable changes in lipid and lipoprotein parameters were seen' with Kliovance. Novo Nordisk alleged that it was misleading to compare dydrogesterone with Kliovance, rather than comparing dydrogesterone with norethisterone acetate, and that this had been done in an unbalanced way; in fact it had been shown that norethisterone acetate opposed the oestrogen-induced rise in triglycerides to a greater extent than dydrogesterone (Godsland 2001).

Novo Nordisk considered that a typical recipient of the leavepiece would be left under the misleading impression that Kliovance had a negative effect on the lipid profile, whereas in fact the effect of Kliovance on the lipid profile was positive or, at worst, neutral. This was a misleading comparison as well as a misrepresentation of the referenced data, and could not be substantiated by the referenced data.

Novo Nordisk provided a copy of its correspondence with Solvay Healthcare and addressed some of the points Solvay Healthcare had made.

Whilst the theory that any positive effect on the lipid profile that was caused by HRT might have a positive effect on the cardiovascular system had not been demonstrated in clinical trials, and remained 'emerging clinical or scientific opinion', it was known that dyslipidaemia was an important risk factor for cardiovascular disease. However there was no consensus as to which lipid fractions were the most important, and it was generally accepted that all parameters would have some significance; HDL, LDL, IDL, total cholesterol, ratios, apoproteins, etc.

Whilst omitting any mention of the negative effect of Femoston-conti on triglyceride levels, Solvay Healthcare had referred to work supporting the use of the total cholesterol/HDL-cholesterol ratio as the preferred ratio for assessing risk, as if it were the consensus of current opinion (Haq *et al* 1999). However, putting aside the fact that cardiovascular risk was obviously more complex than just lipid profile alone, even with regard only to the lipid profile, Novo Nordisk did not accept that HDL or even the total/HDL ratio was accepted as the gold standard in risk prediction. Even a basic search through the more recent literature demonstrated that the jury was still very much out on what lipid fractions were the most significant when it came to risk factors for diseases such as coronary heart disease and stroke (Sposito *et al* 2001, Rizos and Mikhailidis 2001, Samsioe 1993 and Dominiczak 2001).

Additionally, Whitehead (1994), which was referenced to support claims for Femoston-conti, reported the recent, large-scale Gothenberg Heart Study finding that, 'Serum triglyceride concentration was an independent risk factor for mortality in women whereas serum cholesterol concentration was not'.

The small comparative study Solvay Healthcare had referred to (Palin *et al*) was in a sample of type 2 diabetic women, and these findings could not be extrapolated to the general population.

To conclude, Novo Nordisk did not dispute that the information in the leavepiece was factually correct. The company considered that the Samsioe data for Kliovance were portrayed selectively and in an unbalanced way to mislead the reader into believing that Kliovance had a negative effect on the lipid profile and that dydrogesterone gave 'lipid profile enhancement', whereas the evidence referenced did not support such a conclusion. Novo Nordisk alleged that the leavepiece was in breach of Clause 7.2 of the Code.

RESPONSE

Solvay Healthcare noted that there was agreement that Femoston-conti 'had a positive effect overall' (on the lipid profile), as was noted in its summary of product characteristics (SPC), so this did not appear to be in dispute. Therefore, it was puzzling that Novo Nordisk subsequently considered it misleading to omit to mention that Femoston-conti produced a rise in triglycerides since the changes in triglyceride levels observed in the study were not statistically significant. It should be noted that Kliovance also produced a small rise in triglyceride levels in the Samsioe study which was presumably also non-significant. On this basis, any discussion of the role of triglyceride concentration as an independent cardiovascular risk factor was irrelevant. The references quoted to support the role of raised triglycerides as a cardiovascular disease risk factor were also irrelevant in this context. They all showed prevailing elevated triglycerides as being a risk factor, not an oestrogen-induced increase in triglycerides as a risk factor. Elevated triglycerides posed a risk due to their association with other metabolic abnormalities such as impaired glucose tolerance and insulin resistance, and low HDL-cholesterol (Bruneck *et al*, 1998).

Solvay Healthcare noted that Novo Nordisk considered that it was misleading to compare dydrogesterone with Kliovance, rather than comparing dydrogesterone with norethisterone acetate. This was a totally incorrect interpretation of the data. The comparison was of the effects of Femoston-conti with Kliovance. The statement 'Dydrogesterone maintains positive effect of oestrogen on HDL-cholesterol' related to its effect in combination with oestradiol in the Femoston-conti formulation. It could not reasonably be understood to relate to a comparison of the effect of one component of Femoston-conti with Kliovance. This would be pointless and irrelevant to the promotion of Femoston-conti.

The veracity of the claim 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance' was not disputed. Reference to the data appeared in the Kliovance SPC: 'A decrease in HDL values over time was observed without any change in the LDL/HDL ratio'. Solvay Healthcare noted that Novo Nordisk considered that this strongly implied a negative effect on the lipid profile [of Kliovance] in

comparison with dydrogesterone [see above, the comparison was with Femoston-conti], whereas it was simply reporting the actual findings of the study.

The effects of the two products on the lipid profile were clearly set out in their respective SPCs. Femoston-conti reduced total cholesterol and LDL whilst increasing HDL. In contrast, Kliovance reduced total cholesterol, LDL and HDL. Femoston-conti therefore produced a favourable change in the LDL/HDL ratio whereas Kliovance produced no change. The claim by Novo Nordisk that the effect of Kliovance on the lipid profile was positive or, at worst, neutral, was not reflected in the SPC.

Solvay Healthcare agreed that it remained to be established whether or not the effects of HRT on plasma lipids had a positive outcome in terms of reduction of cardiovascular events; therefore no claims were made in this regard. However, effects on plasma lipids might be considered of relevance in the choice of HRT. The company also accepted that there was no absolute agreement about which lipid fractions were the most important as regards cardiovascular risk prevention; however, there was very clear consensus that total cholesterol and HDL levels were important risk predictors. The 'Joint Recommendations of the British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society and British Diabetic Association on Prevention of Coronary Heart Disease in Clinical Practice' coronary risk prediction chart (British Hyperlipidaemia Association, 2000) based dyslipidaemia-associated risk assessment on total cholesterol, HDL and the derived total/HDL-cholesterol ratio, without reference to the triglyceride level.

Solvay Healthcare stated that it was clear that there was a difference in the effect of the two products on the lipid profile which was illustrated by their effects on HDL-cholesterol. Solvay Healthcare considered that it was quite reasonable, in view of the accepted theoretical value of increasing HDL, to point out this difference. Doing so did not misrepresent the data in any way and should not mislead the reader.

In conclusion Solvay Healthcare did not consider the leavepiece to be in breach of Clause 7.2 of the Code.

PANEL RULING

Femoston-conti and Kliovance were both continuous combined HRT preparations; the oestrogen component of both was oestradiol 1mg. The progestogen component in Femoston-conti was dydrogesterone 5mg and in Kliovance it was norethisterone 0.5mg. The Panel noted that although postmenopausal oestrogen raised HDL-cholesterol levels, in combined therapy this effect would be opposed to different extents depending on the type and dose of progestogen co-administered (Godsland 2001).

Section 5.1 of the Femoston-conti SPC headed 'Pharmacodynamic Properties' stated 'Oral administration of oestrogens can have a beneficial effect on the metabolism of lipids and lipoproteins. Treatment with estradiol/dydrogesterone combinations for up to 24 months resulted in a significant decrease in LDL cholesterol levels and a significant increase in HDL cholesterol. Triglyceride levels were raised overall but usually remained within the normal range'.

The corresponding statement in Section 5.1 of the Kliovance SPC stated 'Kliovance has influence on metabolic processes. In placebo-controlled clinical trials, Kliovance reduced total cholesterol, LDL-cholesterol, and lipoprotein (a). A decrease in HDL-cholesterol over time was observed without any change in the LDL/HDL ratio. Kliovance did not increase triglycerides levels. In addition, Kliovance did not alter glucose tolerance or insulin sensitivity'.

The two claims at issue appeared in the leavepiece below a sub-heading of 'Lipid profile enhancement' although both only referred to one part of the plasma lipid profile ie HDL-cholesterol. The Panel did not consider this unacceptable *per se*. Novo Nordisk was concerned that the negative effect of Femoston-conti on triglycerides had not been referred to in the leavepiece. The Panel noted that the Solvay Healthcare study H.102.5011.02 showed that triglyceride levels increased following one year's treatment with Femoston-conti although the mean values always remained within the normal range. This finding was consistent with the statement in the SPC. In the circumstances the Panel did not consider that omission of the triglyceride data was misleading and no breach of Clause 7.2 was ruled in that regard. This ruling was accepted.

The Panel considered that the claim 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance' implied that Kliovance had a negative effect on the plasma lipid profile. The claim was referenced to an abstract by Samsioe *et al*. The authors of that study noted, however, that the LDL/HDL-cholesterol ratio did not change and concluded that favourable changes in lipids and lipoproteins were seen with Kliovance. The Panel noted that similarly the Kliovance SPC also referred to a decrease in HDL-cholesterol over time without any change in the LDL/HDL ratio. The Panel considered that the claim in question did not reflect the whole of the data with regard to the effect of Kliovance on HDL-cholesterol and so was misleading in that regard. A breach of Clause 7.2 was ruled. This ruling was appealed.

The Panel did not consider it was misleading *per se* to compare dydrogesterone with Kliovance as alleged. No breach of Clause 7.2 was ruled. This ruling was accepted.

APPEAL BY SOLVAY HEALTHCARE

Solvay Healthcare stated that the information in the leavepiece was accurate and that it demonstrated in a fair and balanced way that Femoston-conti, in comparison to Kliovance, enhanced the lipid profile by raising the HDL-cholesterol level.

Solvay Healthcare noted that the Panel accepted that postmenopausal oestrogen benefited plasma lipids by raising HDL-cholesterol, and that in combined therapies this effect would be opposed to different

extents dependent on the type and dose of progestogen co-administered. The difference between the two preparations in question was the progestogen: dydrogesterone in Femoston-conti and norethisterone acetate in Kliovance.

Solvay Healthcare stated that the main differences between androgenic and non-androgenic progestogens, when used in combined HRT, on lipids and lipoproteins were their effects on HDL-cholesterol and on triglycerides (Stevenson, 1996; Stevenson, 2000). Comparing the effects of Femoston-conti and Kliovance on lipids and lipoproteins in the studies cited in the leavepiece (Samsioe *et al*; Solvay Healthcare Limited, H102.5011.02), there appeared to be no differences in their effects on triglycerides, and there were no differences in their effects on LDL-cholesterol. Both combinations favourably affected the LDL-cholesterol level. Thus the major difference was the effect on HDL-cholesterol. Femonston-conti resulted in an increase in HDL-cholesterol, whereas Kliovance resulted in a tendency for a decrease. As a result, the LDL/HDL ratio decreased on Femoston-conti but remained unchanged on Kliovance. The lack of change in the LDL/HDL ratio on Kliovance could not be reasonably interpreted as an enhancement of the lipid profile: a favourable change in the LDL/HDL ratio was a decrease, and this was seen with Femoston-conti but not with Kliovance.

Solvay Healthcare noted that the Panel's main concern appeared to be that the leavepiece made no reference to the lack of change in the LDL/HDL ratio on Kliovance. However, since the reason the ratio remained unchanged was that the HDL-cholesterol levels fell, it was as valid to compare changes in HDL levels as it was to compare changes in the ratio. In both instances, Femoston-conti enhanced the lipid profile but Kliovance did not. Solvay Healthcare considered that the claim accurately reflected the whole of the data and that the reader would have gained exactly the same understanding if the LDL/HDL ratio on Kliovance as well the HDL-cholesterol level had been used to illustrate the point.

COMMENTS FROM NOVO NORDISK

Novo Nordisk maintained that the statement 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance', in the context of leavepiece, ie beneath the heading, 'Lipid profile enhancement', misled the reader into the assumption that Femoston-conti enhanced the lipid profile whilst Kliovance had a negative effect. This was an unbalanced and ambiguous presentation of the data, and as such was clearly in breach of Clause 7.2 as ruled by the Panel.

Novo Nordisk was pleased that the Panel agreed that the item implied a negative effect of Kliovance on the lipid profile, and noted that Solvay Healthcare did not dispute this.

Novo Nordisk noted that Solvay Healthcare, in its appeal, stated that the leavepiece demonstrated that Femoston-conti, in comparison with Kliovance, enhanced the lipid profile by raising HDL-cholesterol. Novo Nordisk did not accept that the statement 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance', in this context, gave the reader the impression of a neutral effect of Kliovance on the lipid profile as Solvay Healthcare claimed.

Novo Nordisk did not accept HDL-cholesterol as a proxy for the lipid profile as a whole, and noted that the references cited in its complaint demonstrated that the enhancement or otherwise of the lipid profile did not depend solely on the change in HDL, as was the impression given by this piece. Samsioe 1993 concluded that 'Accumulating evidence suggests that HDL-cholesterol, angiotensin and several of the common, liver-derived clotting factors are misleading and should be abandoned as prime markers for the prediction of clinical outcome in terms of CVD in women on hormone replacement therapy' (Samsioe 1993). In terms of stroke prevention, Rizos and Mikhailidis (2001) concluded that the evidence suggested that not only total cholesterol and LDL but also HDL and triglyceride levels predicted the risk of a cerebrovascular event. The references from Stevenson cited by Solvay Healthcare both stated with regard to the effects of HRT, 'Since it was not known whether the reduction in HDL reflected any impairment in remnant clearance, the clinical significance of lowering HDL remained to be determined'.

The Samsioe *et al* abstract, as well as the Kliovance SPC, referred to no change over time in the LDL/HDL-cholesterol ratio with Kliovance, demonstrating that although HDL-cholesterol tended to fall over time so did LDL-cholesterol and hence the LDL/HDL ratio remained the same. The Kliovance SPC also referred to a neutral effect on triglyceride levels, whereas the Femoston-conti SPC confirmed a rise in triglyceride levels over time, although levels usually remained within the normal range. Had the LDL/HDL ratios been presented in the leavepiece, as Solvay Healthcare suggested in its appeal, it would have given a more balanced account of the data but still an incomplete one, if the title, 'Lipid profile enhancement' was to be used.

As it was generally accepted that there was more to cardiovascular risk than the lipid profile, and that there was more to the lipid profile than the HDL-cholesterol level or indeed the total/HDL ratio, Novo Nordisk referred to the Samsioe abstract (1998) which concluded, taking into account the effects of Kliovance on HDL, LDL, triglycerides, lipoprotein (a) and apolipoprotein B-100, that 'favourable changes were seen in lipid and lipoprotein parameters' after 12 months of Kliovance.

In conclusion, Novo Nordisk did not consider that the reasons given by Solvay Healthcare in its appeal should change the ruling. The new references cited by Solvay Healthcare did not appear to contribute new information to the discussion, and did not change the impression given by the leavepiece to the intended reader, that Kliovance had a negative effect on the lipid profile whilst Femoston-conti had a positive effect. The data presented were misleading due to their incomplete and ambiguous nature, and the leavepiece did not take account of all the evidence available. Novo Nordisk therefore considered that the Panel acted fairly in ruling a breach of Clause 7.2.

APPEAL BOARD RULING

The Appeal Board noted the heading 'Lipid profile enhancement' beneath which the two claims 'Dydrogesterone maintains the positive effect of oestrogen on HDL-cholesterol' and 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance' appeared. The Appeal Board did not agree with Solvay Healthcare's submission that the implied message was that Femoston-conti enhanced the lipid profile and Kliovance did not. The Appeal Board considered that taken together the two claims implied that Femoston-conti had a positive effect on plasma lipids and Kliovance had a negative effect. Although Samsioe *et al* had shown that Kliovance treatment was associated with a decrease in HDL-cholesterol, an effect noted in the Kliovance SPC, the LDL/HDL ratio did not change and this information had not been given. The claim 'HDL-cholesterol tended to decrease after 12 months with Kliovance' did not reflect the whole of the data and thus gave a misleading impression. This was further compounded by the heading 'Lipid profile enhancement'. The claims were limited to the effects of each treatment on HDL-cholesterol whereas the lipid profile was composed of many other lipid fractions.

The Appeal Board considered that the claim 'HDL-cholesterol tended to decrease after 12 months treatment with Kliovance' was misleading and upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

Complaint received **22 February 2002**

Case completed **28 May 2002**

CASE AUTH/1282/2/02

NHS TRUST AUDIT PHARMACIST v WYETH

Prescribing guidance

An NHS trust audit pharmacist complained on behalf of a primary/secondary care pharmacists group about the covering letter which was sent with '[local] Prescribing Guidance – a 'NICE' approach to Proton Pump Inhibitors'. The guidance was produced by members of the group with specialist input from the lead gastrointestinal pharmacist and gastrointestinal medical consultants at a local teaching hospitals trust. The final copy was given to Wyeth to be printed. Throughout discussions with Wyeth it was made clear the company could not have influence over the content.

The group was most surprised to see that in the covering letter Wyeth had referred to itself and two named pharmacists as being involved in the development of the guidance. This was clearly untrue and contradicted the statement printed at the bottom: 'This document was written by doctors and pharmacists [locally]. It has been printed with the support of Wyeth Laboratories, who had no influence on its contents'. The group was concerned that Wyeth's representatives were giving this information to GPs and pharmacists.

The Panel noted that the covering letter accompanied bulk deliveries of the guidance to eight individuals; it had not been generally distributed. Wyeth had verbally instructed its printers to insert the short cover note and the printers acknowledged that the verbal instruction was not accurately translated. The Panel was concerned that Wyeth had not confirmed these instructions in writing and nor had it sought sight of the covering letter prior to its distribution. The covering letter inaccurately described the guidance. The Panel considered that high standards had not been maintained and a breach of the Code was ruled.

The audit pharmacist of a community and mental health services NHS trust complained on behalf of a primary/secondary care pharmacists group to Wyeth about a covering letter which was sent with '[local] Prescribing Guidance – a 'NICE' approach to Proton Pump Inhibitors'. A copy of the letter to Wyeth was sent to the Authority and taken up as a complaint under the Code.

COMPLAINT

On behalf of the primary/secondary care pharmacists group the complainant thanked Wyeth for printing the guidance for distribution to local doctors and pharmacists and reminded the company of the process used to develop it. The proton pump inhibitor (PPI) guidance was produced by members of the group with specialist input from the lead gastrointestinal pharmacist and gastrointestinal medical consultants at a local teaching hospitals trust. Following this, the document was consulted in primary care before the final copy was presented to the local prescribing committee for approval. The final copy was then given to Wyeth to be printed.

Throughout the group's discussions with Wyeth it was made clear that the company could not have influence over the content although it was agreed that the statement 'NICE recommends using the cheapest PPI that is licensed for the relevant indication' could be added following its suggestion. The group considered it to be an omission that needed to be included in the document to reflect the NICE recommendations accurately.

The group was most surprised to see that on the covering letter enclosed with the distributed guidance Wyeth included itself as being involved in the development of the guidance and only mentioned two

of the pharmacists involved with the project. The letter read 'Please find enclosed your copies of '[local] Prescribing Guidance – a 'NICE' approach to Proton Pump Inhibitors' and referred to its development by a member of a hospital pharmacy department, a PCG prescribing advisor and a healthcare development manager at Wyeth.

This statement was clearly untrue. The two pharmacists mentioned were not happy to be named in this way and it had offended all those actually involved but not named. It was totally unacceptable for Wyeth to claim credit for the work. Not only did this undermine the autonomy of the guidance, it also contradicted the statement printed at the bottom: 'This document was written by doctors and pharmacists [locally]. It has been printed with the support of Wyeth Laboratories, who had no influence on its contents'.

The pharmacists group was concerned that Wyeth's representatives were giving this information to GPs and pharmacists and considered this was in breach of a verbal understanding and industry standards.

When responding to this complaint Wyeth was asked to bear in mind the requirements of Clauses 7.2, 9.1 and 2 of the Code.

RESPONSE

Wyeth gave its assurance that it was never its intention to claim any involvement in the development of the guidance. As the complainant noted this would contradict the statement printed at the bottom of the guidance that the document was written by local doctors and pharmacists, with Wyeth having no influence on its content.

Wyeth stated that there appeared to have been a gross misunderstanding between the company and its printers/bulk distributors in respect of the wording on the cover note supplied with the guidance, in connection with its initial bulk distribution to eight specified individuals, one of whom was the complainant. Copies of a letter from Wyeth to the complainant explaining the circumstances of the covering letters, and of an apology from the printers, were enclosed.

Wyeth stated that it had briefed the printers to attach a courteous cover note to the bulk delivery packs of the guidance dispatched by it to each of the eight recipients. The printers were instructed verbally to the effect 'Please find enclosed the '[local] Prescribing Guidance – a NICE approach to PPIs'. [The] healthcare development manager, Wyeth has liaised with [pharmacists] re printing and design concepts of the enclosed document'. There was never any mention that wording should be included relating to the involvement of Wyeth, or indeed of any individuals, in the development of the guidance. In its apology, the printers fully acknowledged that the verbal instruction issued by Wyeth was not accurately translated onto the cover note.

In its letter to the complainant, Wyeth reassured her that the inadvertent claim of its involvement in the development of the guidance contained in the cover note had not been disseminated to GPs and pharmacists by any Wyeth representative in any form whatsoever. The cover note was only used in association with the distribution of bulk supplies of the guidance to the eight specified individuals. Local distribution of the guidance was the sole responsibility of each of the named recipients of the bulk supplies.

Wyeth considered that this was an unintentional error, arising from a misunderstanding between the company and its printers. Both parties had apologised to the complainant and reassured her that this was an isolated incident occurring during the distribution of bulk copies of the guidance.

Wyeth had admonished the individuals responsible for the breakdown in communication and taken appropriate steps to ensure that similar problems did not arise in the future.

In the circumstances, Wyeth denied breaches of Clause 7.2, Clause 9.1 and in particular Clause 2.

PANEL RULING

The Panel noted that the covering letter at issue accompanied bulk deliveries of the guidance to eight individuals; it had not been generally distributed. Wyeth stated that it had verbally instructed its printers to insert a short cover note to accompany the bulk deliveries. The printers acknowledged that the verbal instruction was not accurately translated onto the cover note. The Panel was concerned that Wyeth had not confirmed these instructions in writing nor had it sought sight of the covering letter prior to its distribution. The covering letter inaccurately described the guidance. The Panel considered that high standards had not been maintained; a breach of Clause 9.1 was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of either Clause 7.2 or Clause 2 of the Code; no breach of those clauses was ruled.

Complaint received **28 February 2002**

Case completed **3 May 2002**

CASE AUTH/1283/2/02

DERMAL LABORATORIES v CROOKES HEALTHCARE

Promotion of Unguentum M

Dermal Laboratories complained about a journal advertisement for Unguentum M by Crookes Healthcare which featured an illustration of a tube of the product beneath which was the word 'unique' in bold prominent type. The text stated 'Unguentum M is the only ambiphilic emollient available. That means it works like an ointment, but vanishes like a cream'. Dermal marketed Doublebase which was also an emollient; its gel formulation also functioned as a true ointment on the skin. Dermal therefore challenged the statement that Unguentum M was unique because it worked like an ointment but vanished like a cream.

The Panel noted that the Unguetum M summary of product characteristics (SPC) described the product as an ambiphilic, topical preparation with emollient properties, which maintained the high lipid content of an ointment but also had the water miscible characteristics of a cream. The Doublebase SPC stated that the oily ingredient encouraged rehydration by forming an occlusive barrier within the skin surface (stratum corneum) thus reducing drying and skin greasiness. The product was described as relatively non-greasy despite its high oil content.

Both Unguentum M and Doublebase were emollient preparations and both produced a barrier of lipids within the skin to reduce water loss. The Panel accepted that although Unguentum M was described as ambiphilic, and Doublebase was described as relatively non-greasy, most prescribers would regard both products as having the properties of an ointment without the greasiness normally associated with such preparations. The Panel considered that it was misleading and exaggerated to refer to Unguetum M as the only ambiphilic emollient available that 'works like an ointment, but vanishes like a cream' and to describe it as 'unique' in that regard. Breaches of the Code were ruled.

Dermal Laboratories Limited complained about a journal advertisement for Unguentum M (ref CHCSK01-142-B) issued by Crookes Healthcare Ltd. The advertisement featured an illustration of a tube of the product standing on its cap beneath which was the word 'Unique' in bold prominent type. Text beneath stated 'Unguentum M is the only ambiphilic emollient available. That means it works like an ointment, but vanishes like a cream'. Dermal marketed Doublebase which was also an emollient.

COMPLAINT

Dermal stated that most, if not all, aqueous creams worked like an ointment, but vanished like a cream. The continuous aqueous phase allowed the cream to be absorbed, particularly into dry skin, and after this evaporated the residual oily phase remained within the skin to function as an 'ointment'. The problem was that the oily residue remaining could still be re-emulsified with water so that the absorbed 'ointment' was easily removable, either through sweating or by washing, showering and bathing. As this applied to Unguentum M, it was therefore not true to claim that the absorbed residue worked like a true ointment.

Dermal marketed an emollient called Doublebase which had been specifically designed as a viscous aqueous gelled emulsion. Immediately on absorption into dry skin, the emulsion system broke, separating irreversibly into two phases. This allowed the lipid phase to be released for emolliation and the aqueous phase for moisturising the skin. Since the oily phase could not be re-emulsified with water, the barrier effect was retained even with gentle washing, showering or bathing. Unlike Unguentum M, Doublebase certainly functioned as a true ointment in the skin.

Dermal therefore challenged the statement that Unguentum M was 'unique' because it worked like an ointment, but vanished like a cream. Breaches of Clauses 7.2, 7.4 and 7.10 of the Code were alleged.

RESPONSE

Crookes Healthcare stated that the promotional campaign featured a number of different advertisements and was based upon a play on words involving the rather unusual name of the product, which some people found difficult to spell.

Alleged breach of Clause 7.10 Crookes Healthcare stated that this clause related to the use of superlatives, exaggerated or all-embracing claims, unless the terms could be substantiated as a simple statement of fact which could be clearly demonstrated. The words to which Dermal objected were 'Unique' and 'the only' when applied to Unguentum M, as used for example, in the phrase 'the only ambiphilic emollient'.

Use of the word 'unique' was, in Crookes Healthcare's view, justified as a simple statement of fact in that Unguentum M was a unique formulation. It could also be applied to Dermal's product, Doublebase, which was again a unique formulation. Different emollients had quite specific formulations and could not be regarded as directly equivalent in the way that, for example, tablets containing the same amount of a recognised active ingredient might be regarded as equivalent.

Use of 'the only' was used in the context of Unguentum M being 'the only ambiphilic emollient'. The term 'ambiphilic' was not found in standard dictionaries but was used in a specialist context, particularly in polymer chemistry. In simple terms, it meant a combination of lipophilic and hydrophilic characteristics. Crookes Healthcare did not claim that Unguentum M separated into two phases on the skin, but that it remained on the skin as a single emulsion with atypical physical characteristics. This enabled the product to spread like a cream, but have a high lipid content like an ointment.

Dermal had claimed that its Doublebase had been designed as a viscous aqueous gelled emulsion and that on the skin the product broke into two phases. Dermal had further stated that it did not believe that the oily phase of Unguentum M worked like a true ointment, but that Doublebase did function in this way.

Unfortunately, Dermal had not provided any evidence in support of its assertion that Doublebase was ambiphilic as described above. The packaging and summary of product characteristics (SPC) were silent on the mode of action. The product description on the pack read 'highly moisturising and protective hydrating gel' but made no reference to two phases working on the skin.

In contrast, the approved packaging for Unguentum M described the product as 'Ambiphilic Dermatological Cream', and the SPC stated in section 5.1 'Unguentum M is an ambiphilic topical preparation with emollient properties which maintains the high lipid content of an ointment but also has the water miscible characteristics of a cream'.

In view of the fact that Crookes Healthcare had not seen any substantiation of Dermal's assertion that Doublebase was ambiphilic in the same way as Unguentum M, it was unable to change its view that use of terms such as 'the only' were still supportable for its product.

Alleged breach of Clause 7.2 Crookes Healthcare stated that this clause covered misleading information, claims and comparisons. For the reasons given above, Crookes Healthcare did not believe that it had presented misleading information on Unguentum M. Dermal had not presented any evidence that invalidated the statements given in the promotional material. The SPC supported the claims of ambiphilic action and the dual ointment/cream mode of action. Until such time as evidence of Doublebase's mode of action was available to Crookes Healthcare, it believed that Unguentum M remained the only ambiphilic emollient on the UK market.

Alleged breach of Clause 7.4 Crookes Healthcare believed that it had substantiated its information and claims. Comparisons had not been made.

PANEL RULING

The Unguentum M SPC described the product as a cream. Section 5.1, Pharmacodynamic Properties, stated that it was an ambiphilic, topical preparation with emollient properties which maintained the high lipid content of an ointment but also had the water miscible characteristics of a cream. The high lipid content reduced water loss from the skin and therefore had a hydrating effect. Doublebase was described in its SPC as a gel. In the section describing the pharmacodynamic properties it was stated that the oily ingredients, isopropyl myristate and liquid paraffin, encouraged rehydration and softening of dry skin by forming an occlusive barrier within the skin surface, thus reducing drying from evaporation of water that diffused from the underlying layers. A description of the pharmacokinetic properties stated that because Doublebase was designed to deliver the emollient ingredients into the stratum corneum when gently applied to areas of dry skin, it was relatively non-greasy despite its high oil content.

The advertisement in question stated 'Unguentum M is the only ambiphilic emollient available. That means it works like an ointment, but vanishes like a cream'. Both Unguentum M and Doublebase were emollient preparations and both produced a barrier of lipids within the skin to reduce water loss. The physical way in which the products achieved this differed. The Panel accepted that Unguentum M was actually described in its SPC as ambiphilic whereas Doublebase was described only as relatively non-greasy but considered that most prescribers would regard both products as having the properties of an ointment without the greasiness normally associated with the use of such preparations. On balance the Panel considered that it was misleading and exaggerated to refer to Unguentum M as the only ambiphilic emollient available that 'works like an ointment, but vanishes like a cream' and to describe it as unique in that regard. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

The Panel noted Crookes Healthcare's submission that use of the word 'unique' was justified as a simple statement of fact in that Unguentum M was a unique formulation as was Doublebase. The supplementary information to Clause 7.10 of the Code referred, *inter alia*, to the use of the word 'unique' and stated that great care needed to be taken with its use. Although in some circumstances the word might be used to describe some clearly defined special feature of a medicine, in many instances it might simply imply general superiority. In such circumstances it was not possible to substantiate the claim as the claim itself was so ill defined. In the Panel's view simply to describe the formulation of a medicine as unique was not acceptable as that would mean that almost all medicines could be described as such.

Complaint received **28 February 2002**

Case completed **26 April 2002**

CASES AUTH/1284/3/02 and AUTH/1306/4/02

MERCK SHARP & DOHME v BRISTOL-MYERS SQUIBB and SANKYO PHARMA

Promotion of Lipostat

Merck Sharp & Dohme complained about two Lipostat (pravastatin) leavepieces issued jointly by Bristol-Myers Squibb and Sankyo Pharma.

With regard to the claim 'USE pravastatin – the only statin consistently proven to prevent heart attacks and strokes in patients with CHD', Merck Sharp & Dohme stated that the 4S study and more recently the Heart Protection Study had shown that in patients with coronary heart disease (CHD) its product simvastatin (Zocor) could prevent heart attacks and stroke. Whilst the company did not currently have a licence in the UK for stroke reduction in patients with CHD and therefore did not make this claim, it did have the data.

The Panel accepted that, on the basis of the material before it, when the leavepiece was prepared (April 2000) the claim 'USE pravastatin – the only statin consistently proven to prevent heart attacks and strokes in patients with CHD' was not misleading. The Heart Protection Study, however, had shown that simvastatin also prevented heart attacks and strokes. The Panel noted Bristol-Myers Squibb and Sankyo's submission that they had been unaware of the results from the Heart Protection Study until a press release issued at the American Heart Association's meeting in November 2001 had been provided to them by the Authority when it had notified them of the complaint; on receipt of the press release the companies had ceased using the leavepiece. It was incumbent upon companies to ensure that they were aware of new clinical data as it became available. The Panel noted that Bristol-Myers Squibb referred to the results of the Heart Protection Study in a letter to Merck Sharp & Dohme dated 19 February 2002. The Panel found it difficult to accept that Bristol-Myers Squibb and Sankyo were not aware that the results of the Heart Protection Study were presented at the American Heart Association meeting in November 2001. With the release of data from the Heart Protection Study the claim was misleading and exaggerated. Breaches of the Code were ruled.

Merck Sharp & Dohme alleged that a leavepiece with a table showing the licensed clinical endpoints of pravastatin simvastatin and other statins had the potential to mislead physicians, by using the word 'Licensed' at the start of the title, into thinking that the table was comparing licensed indications not study endpoints.

The Panel considered that it was unclear as to what the title 'Licensed clinical endpoints' referred; the title was misleading and ambiguous in that regard. In the Panel's view some readers would assume it meant 'Licensed indications' and that appeared not to be so. The Panel considered that the title was confusing and the comparison of data subsequently misleading. A breach of the Code was ruled.

Merck Sharp & Dohme Limited complained about two Lipostat (pravastatin) leavepieces (refs LIP 504 and LIP 538) issued jointly by Bristol-Myers Squibb Pharmaceuticals Limited and Sankyo Pharma UK Limited. Merck Sharp & Dohme marketed Zocor (simvastatin).

Bristol-Myers Squibb and Sankyo submitted a joint response.

1 Claim 'USE pravastatin – the only statin consistently proven to prevent heart attacks and strokes in patients with CHD'

This claim appeared in the leavepiece ref LIP 504.

COMPLAINT

Merck Sharp & Dohme alleged that the claim was disparaging and potentially misleading to physicians. The 4S study and more recently the Heart Protection Study (HPS) had shown that in patients with coronary heart disease (CHD) simvastatin could prevent heart attacks and stroke. Whilst the company did not currently have a licence in the UK for stroke reduction in patients with CHD and therefore did not make this claim, it did have the data.

In intercompany dialogue Bristol-Myers Squibb had claimed that the leavepiece was released in May 2000 and at that time pravastatin was the only statin to have two large studies demonstrating these endpoints, CARE and LIPID. In accordance with Clause 7.2 of the Code, claims and comparisons must be based on an up-to-date evaluation of all the evidence and clearly reflect that evidence. In light of the results from the recent large scale HPS this leavepiece was clearly no longer accurate.

Bristol-Myers Squibb had also stated that because simvastatin was not licensed for stroke reduction in the UK, this claim as stated was a fair representation. Merck Sharp & Dohme noted that the claim was not that pravastatin was the only statin licensed to prevent heart attack and stroke; it was that it was 'the only statin consistently proven to prevent heart attacks and strokes in patients with CHD' which was for the reasons stated above clearly not the case. Merck Sharp & Dohme alleged breaches of Clauses 7.2 and 7.10 of the Code.

RESPONSE

Bristol-Myers Squibb and Sankyo noted that a copy of the press release for the HPS, which unfortunately was not provided to them by Merck Sharp & Dohme when it originally raised its concerns about the leavepiece in February 2002, had been provided with the notice of the complaint. Having now had the opportunity to review the press release, the companies confirmed that they agreed to cease using the leavepiece immediately. They would also undertake a review of all current Lipostat promotional materials to ensure the same claim was not made elsewhere. They became aware of the press release for the first time when they received the letter

from the Authority informing them of the complaint. Since Merck Sharp & Dohme did not share this information with them when it contacted them in February 2002 they were denied the information that would have enabled them to determine the fairness and accuracy of their leavepiece. Bristol-Myers Squibb and Sankyo therefore did not accept that, with the information they had in February, they were in breach of Clauses 7.2 and 7.10 as alleged.

PANEL RULING

The leavepiece at issue was prepared in April 2000; this was before the results of the HPS were known. According to the press release provided by Merck Sharp & Dohme the key results of the HPS were unveiled at the American Heart Association's Scientific sessions on Tuesday, 13 November, 2001. One of the key findings from the study was that cholesterol lowering with statin treatment reduced the risk of heart attacks and of strokes by at least one third. The statin used in the HPS was simvastatin. The earlier 4S study, the results of which were published in November 1994, showed that there were significantly fewer fatal plus non-fatal cerebrovascular events in the simvastatin group than in the placebo group (70 vs 98 respectively; p=0.024). These results were, however, obtained from a post-hoc analysis and were not part of the primary analysis.

The Panel accepted that, on the basis of the material before it, when the leavepiece was prepared the claim 'USE pravastatin – the only statin consistently proven to prevent heart attacks and strokes in patients with CHD.' was not misleading. The HPS, however, had shown that simvastatin also prevented heart attacks and strokes. The Panel noted that Merck Sharp & Dohme did not currently have a UK licence for stroke reduction and the company's submission that it did not make such a claim in the UK. The Panel noted Bristol-Myers Squibb and Sankyo's submission that they had been unaware of the results from the HPS until the press release had been provided to them by the Authority when it had notified them of the complaint and on receipt of the press release the companies had ceased using the leavepiece. The Panel considered it was incumbent upon companies to ensure that they were aware of new clinical data as it became available and noted that in that regard the press release had been issued at a major scientific conference. The Panel noted that Bristol-Myers Squibb referred to the results of the HPS in a letter to Merck Sharp & Dohme dated 19 February 2002. The Panel found it difficult to accept that Bristol-Myers Squibb and Sankyo were not aware that the results of the HPS were presented at the American Heart Association meeting. With the release of data from the HPS the claim was misleading and exaggerated. Breaches of Clauses 7.2 and 7.10 were ruled.

2 Licensed clinical endpoints

Leavepiece LIP 538 included a table to show the licensed clinical endpoints of pravastatin (recurrent MI, total mortality, PTCA/CABG, stroke (post-MI), first MI, reduction in days of hospitalisation), simvastatin (recurrent MI, total mortality, PTCA/CABG) and other statins (none of the licensed clinical endpoints listed was ticked).

COMPLAINT

Merck Sharp & Dohme stated that by using the word 'Licensed' at the start of the title, this had the potential to mislead physicians into thinking that the table was comparing licensed indications not study endpoints.

In intercompany dialogue Bristol-Myers Squibb had claimed that the table was meant to refer to clinical endpoints for which statins were licensed to reduce the risk. Merck Sharp & Dohme had no objection to that, but it did not consider that the wording of the title made this clear. A breach of Clause 7.3 of the Code was alleged.

RESPONSE

Bristol-Myers Squibb and Sankyo did not agree that the title of the table was misleading and considered that it was unreasonable to suggest that a physician would misinterpret 'Licensed clinical endpoints'. How could 'Reduction in days of hospitalisation' be misconstrued as a licensed indication, when it was clearly not a clinical condition? The companies suggested that the only way that the table could be read was as a comparison of the clinical endpoints that the statins were licensed to prevent. The companies therefore refuted the allegation that the title of the table was in breach of Clause 7.3 of the Code.

PANEL RULING

In the Panel's view 'Licensed clinical endpoints' would be read to mean licensed indications. Zocor (simvastatin) was licensed in coronary heart disease to: reduce risk of mortality; reduce the risk of coronary death and non-fatal myocardial infarction; reduce the risk for undergoing myocardial revascularisation procedures (CABG and PTCA); slow the progression of coronary atherosclerosis, including reducing the development of new lesions and new total occlusions (ref summary of product characteristics). The 'Licensed clinical endpoints' ticked for simvastatin on the leavepiece were recurrent MI, total mortality and PTCA/CABG. There was no mention of slowing the progression of coronary atherosclerosis.

The Panel considered that it was unclear as to what the title 'Licensed clinical endpoints' referred; the title was misleading and ambiguous in that regard. In the Panel's view some readers would assume it meant 'Licensed indications' and that appeared not to be the case. One of the licensed cardiovascular indications for Zocor was not included in the table of data. The Panel considered that the title was confusing and the comparison of data subsequently misleading. A breach of Clause 7.3 was ruled.

Complaint received **4 March 2002**

Case completed **13 May 2002**

CASE AUTH/1285/3/02

MEDIA/DIRECTOR v PFIZER

Lipitor journal advertisement

A letter in The Pharmaceutical Journal criticised a Lipitor (atorvastatin) advertisement issued by Pfizer which had appeared in a previous edition of the journal. In accordance with established practice, the matter was taken up as a complaint. The advertisement headed 'Heart Protection Study could open statin floodgates' discussed the results of the Heart Protection Study.

The author of the published letter stated that the advertisement opened in bold type with 'All patients at high risk of CHD benefit from statins'. The author referred to the fact that the Medicines Control Agency had drawn attention to the withdrawal of Lipobay and had stated that all statins had been associated with a risk of muscle disorders including rhabdomyolysis. The British National Formulary 'advised patients to report promptly unexplained muscle pain, tenderness and weakness'. The author further stated that deaths attributable to Lipobay notified to the Committee on Safety of Medicines (CSM) had almost doubled since last year, and the CSM had all the statins under review.

The author questioned whether the claim that all patients benefit could be justified.

The Panel noted that beneath the heading 'All patients at high risk of CHD benefit from statins' the advertisement stated that the Heart Protection study had '… shown that many more patients would benefit from cholesterol lowering with a statin than are currently receiving these drugs' and discussed treatment in patients at high risk of cardiovascular disease or with established coronary heart disease. Another section, headed 'Evidence for Lipitor safety', stated '… Lipitor also has clinical trial and real-world data to confirm its safety. In an overview of Lipitor clinical trials only 2% of patients withdrew from treatment due to side-effects'. The Lipitor summary of product characteristics (SPC) stated that the risk of myopathy during treatment with Lipitor might be increased with concurrent administration of certain other drugs. As with other drugs in this class rhabdomyolysis with acute renal failure had been reported. Lipitor was contraindicated in certain patients.

The Panel considered that the heading 'All patients at high risk of CHD benefit from statins' gave the impression that statins were suitable for all high risk CHD patients and that was not necessarily so. There were some patients for whom statins in general and Lipitor in particular were contraindicated. The heading was misleading, all embracing and not capable of substantiation. Breaches of the Code were ruled.

A letter headed 'Are statins really for everybody?' published in The Pharmaceutical Journal on 9 March was critical of an advertisement for Lipitor (atorvastatin) published in that journal by Pfizer Limited on 26 January. A response from Pfizer was also published. In accordance with established practice, the matter was taken up by the Director as a complaint under the Code of Practice.

The advertisement at issue consisted of columns of text and tables of data; it was headed 'Advertisement Feature'. The advertisement was headlined 'Heart Protection Study could open statin floodgates' and discussed the results of the Heart Protection Study. The first paragraph was headed 'All patients at high risk of CHD benefit from statins'.

COMPLAINT

The author of the published letter stated that the advertisement opened in bold type with 'All patients at high risk of CHD benefit from statins'. The Medicines Control Agency's Current Problems in Pharmacovigilance (August 2001) drew attention not only to the withdrawal of Lipobay [another company's statin] but stated that all statins had been associated with a risk of muscle disorders including myopathy and rhabdomyolysis. The British National Formulary under 'side effects' included a counselling statement, 'advise patients to report promptly unexplained muscle pain, tenderness and weakness'. Deaths attributable to Lipobay notified to the Committee on Safety of Medicines (CSM) had almost doubled since last year, and the CSM had all the statins under review.

The author's late father had been prescribed a statin (Lipitor) the previous year and experienced intense muscular pain and elevated temperature two hours after the first dose. The matter was reported to the company and the CSM. Could the words 'all patients benefit' in this advertisement be justified? Perhaps many patients did, but certainly not all.

When writing to Pfizer the Authority asked it to respond in relation to the requirements of Clauses 7.2, 7.4 and 7.10.

RESPONSE

Pfizer stated that the advertisement at issue was produced to announce the price change of atorvastatin. As a result of an informal complaint from another pharmaceutical company, Pfizer withdrew the advertisement from circulation on 24 January.

The letter to The Pharmaceutical Journal expressed concern about the use of the words 'All patients at high risk of CHD benefit from statins'. At the request of the journal, Pfizer had responded and part of the correspondence was published by the journal.

Pfizer did not consider the claim in question to be in breach of Clauses 7.2, 7.4 and 7.10 of the Code; it was not an all-embracing claim for atorvastatin, but was instead part of what was a widely held medical opinion about this class of medicine.

The phrase 'All patients at high risk of CHD benefit from statins' was a generic statement, which did not make any claims for atorvastatin and referred to the

cholesterol lowering ability of this class of medicine. It was based on an assessment of the current medical literature, the reportage of the Heart Protection Study and of current UK guidelines. It was also clear from the advertorial that the first part of the piece referred to statins in general and the later part of the article referred to atorvastatin specifically.

Current Medical Literature

Two recent articles concluded with following statements:

'… Clinical Trials with statins have demonstrated the benefits of cholesterol lowering in both primary and secondary prevention of cardiovascular events…', '… Therefore there is a real value in lowering cholesterol in all those at risk of coronary disease …' (La Rosa 1999).

'… In summary, the benefits of LDL-C [cholesterol] lowering induced by statins appear to be universal, not defined by age or sex. It is important now to work to extend these benefits to all who are at risk for atherosclerotic disease …' (La Rosa *et al* 1999).

A meta-analysis of intervention trials in patients with type 2 diabetes mellitus concluded that '… current trial evidence indicates that treatment of hyperlipidaemia (and hypertension) results in large cardiovascular benefits for patients with type 2 diabetes …, aggressive lipid-lowering and blood pressure lowering is central to prevention of macrovascular complications' (Huang *et al* 2001).

A recently published Drugs and Therapeutics Bulletin focussed on statin therapy and would have been distributed to all UK doctors and pharmacists. In the section of the piece titled 'Who should receive statins', the authors stated:

'… to ensure that all those with an absolute risk [of atherosclerotic disease, such as CHD] above 30% over 10 years receive optimum statin therapy …'.

In a press-release that accompanied the Drugs and Therapeutics Bulletin the following statement was made: '… Statins should be used to treat all patients with atherosclerotic disease, for example those who have already had a heart attack, and those whose risk of developing CHD exceeds 30% over 10 years …'.

Reportage from recently presented Heart Protection Study:

The Heart Protection Study was first presented at the American Heart Association in November 2001. A web-site freely accessible to the public summarised the results of the study, and also provided quotes from investigators and key opinion leaders for the press. The following quotes were taken from this web-site (accessed on 21 March):

'Irrespective of the blood cholesterol levels, a statin should now be considered for anybody with a history of heart disease, stroke, other occlusive vascular disease or diabetes' – HPS statistician, Professor Richard Peto.

'The BHF [British Heart Foundation] welcomes the results of this large study. They are clear and represent a major step forward in the fight against diseases of the heart and circulation – Britain's biggest killers. They emphasise the importance of prevention and extend the range of people who benefit from statin therapy' – Professor Sir Charles George, Medical Director of the British Heart Foundation.

'The results of this important seven year study are great news and will bring real benefits for the many people who are affected by cardiovascular problems. It is particularly good to know that through a single trial we have identified a whole new set of patients with a variety of conditions who can also be treated successfully with statins …' – Professor Sir George Radda, Chief Executive of the Medical Research Council.

'This study will have an enormous impact around the entire world. It has provided the first clear proof that anyone at high-risk stands to benefit irrespective of age, sex or cholesterol level' – Professor Anthony Keech, NHMRC Clinical Trials Centre, Sydney, and Consultant Cardiologist at the Royal Prince Alfred Hospital in Sydney.

Clinical and National Guidelines

The Joint British Recommendations for Prevention of Coronary Heart Disease discussed lipid-lowering treatment in some detail. They concluded that 'In primary prevention it would be appropriate to treat (with lipid-lowering therapy – including statins) those whose CHD risk is 30% or greater over the next 10 years …'.

The National Service Framework (NSF) for CHD recommended treatment for certain groups of at risk patients.

The indications for treatment listed by the document included patients with: A level of blood-pressure alone that conveyed a significant cardiovascular risk; the presence of pre-existing target organ damage (LVH, retinopathy, renal impairment, or proteinuria dose); and an absolute CHD risk of 30%.

The NSF made recommendations for treatment of raised lipids and concluded that reducing cholesterol should be achieved using dietary modifications as first line '… although the majority will also require treatment. Treatment should be with a statin …'.

Pfizer therefore submitted that the line 'All patients at high risk of CHD benefit from statins' was capable of substantiation, was accurate, fair, objective, and not exaggerated when concerning the class of medicine, and therefore not in breach of Clauses 7.2, 7.4 and 7.10. In addition, Pfizer believed that information about atorvastatin's efficacy, safety and price in the advertisement was capable of substantiation.

PANEL RULING

The Panel noted that beneath the heading 'All patients at high risk of CHD benefit from statins' the advertisement stated that the Heart Protection study had '… shown that many more patients would benefit from cholesterol lowering with a statin than are currently receiving these drugs' and discussed treatment in patients at high risk of cardiovascular

disease or with established coronary heart disease. The next section referred to the price reduction of Lipitor. Another section, headed 'Evidence for Lipitor safety', stated '… Lipitor also has clinical trial and real-world data to confirm its safety. In an overview of Lipitor clinical trials involving 2502 patients only 2% of patients withdrew from treatment due to side-effects'. Reference was made to Lipitor's 20 million patient-years' experience. The Panel noted Section 4.4 of the Lipitor summary of product characteristics (SPC) stated that the risk of myopathy during treatment with Lipitor may be increased with concurrent administration of certain other drugs. As with other drugs in this class rhabdomyolysis with acute renal failure had been reported. Section 4.8 headed 'Undesirable effects' stated that Lipitor was generally well-tolerated. Adverse events had usually been mild and transient. The most frequent (1% or more) adverse events associated with Lipitor therapy in patients participating in controlled clinical studies were constipation, flatulence, dyspepsia, abdominal pain, headache, nausea, myalgia, asthenia, diarrhoea and insomnia. Section 4.3 stated that Lipitor was contraindicated in certain patients.

The Panel considered that the heading 'All patients at high risk of CHD benefit from statins' gave the impression that statins were suitable for all high risk CHD patients and that was not necessarily so. There were some patients for whom statins in general and Lipitor in particular were contraindicated. The heading was misleading, all embracing and not capable of substantiation. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

Proceedings commenced 13 March 2002

Case completed 30 May 2002

CASE AUTH/1286/3/02

GENERAL PRACTITIONER v AVENTIS PHARMA

Omission of non-proprietary name

A general practitioner complained about a 'Dear Doctor' letter for Tritace (ramipril), from Aventis Pharma, which announced the launch of the new Tritace Titration Pack. The front page of the letter bore the name Tritace nine times but there was no mention of the approved name, which the complainant suspected was a breach of the Code.

The Panel noted that the letter referred to the licensing of Tritace for cardiovascular risk reduction and the prescribing information on its reverse set out the full indications. In addition, the letter made a number of product claims when setting out the primary study endpoints (relative risk reductions v placebo) in the HOPE study. The inclusion of product claims meant that, contrary to Aventis' submission, the letter was subject to the Code and should have borne the non-proprietary name of the product immediately adjacent to the most prominent display of the brand name. The Panel considered that the most prominent display of the brand name was that in the heading of the letter itself. The non-proprietary name had not been provided there and the Panel accordingly ruled that there had been a breach of the Code.

A general practitioner complained about a 'Dear Doctor' letter (ref TRI: 0230202) for Tritace (ramipril) which he had received from Aventis Pharma Ltd. The letter announced the launch of the new Tritace Titration Pack.

COMPLAINT

The complainant stated that the front page of the letter bore the name Tritace nine times but there was no mention of the approved name. The complainant suspected that omitting the approved name from the front of the letter was a breach of the Code.

RESPONSE

Aventis Pharma stated that it had carefully reviewed the letter and had a number of comments to make.

The letter was to inform prescribers of the availability of a specific pack. The pack had been produced to mirror the dose escalation within the HOPE (Heart Outcomes Prevention Evaluation) study and as such, the end points from the HOPE study were summarised and referenced. Because the letter had been written to provide prescribing information for a specific pack, in Aventis' view it fell outside the definition of a promotional item. Clause 1.2 of the Code specified that 'factual, accurate, informative announcements and reference material concerning licensed medicines and relating, for example, to pack changes …' were not included in the scope of the Code. In order to provide further information to health professionals Aventis had included the abbreviated prescribing information on the reverse of the letter. The generic name ramipril was clearly included within this.

Aventis therefore did not believe that the letter was in breach of the Code.

PANEL RULING

The Panel noted that Aventis had not quoted in full the exemption from the requirements of the Code to which it had referred. The relevant section of Clause 1.2 of the Code went on to make the proviso '… provided that they make no product claims'.

The letter itself referred to the licensing of Tritace for cardiovascular risk reduction and the prescribing

information on its reverse set out the full indications. In addition, the letter made a number of product claims when setting out the primary study endpoints (relative risk reductions v placebo) in the HOPE study. For example, reduction of MI, stroke or death from cardiovascular causes by 22%.

The inclusion of product claims meant that the letter was subject to the Code and should have borne the non-proprietary name of the product immediately adjacent to the most prominent display of the brand name. The Panel considered that the most prominent display of the brand name was that in the heading of the letter itself. The non-proprietary name had not been provided there and the Panel accordingly ruled that there had been a breach of Clause 4.3.

Complaint received **13 March 2002**

Case completed **4 April 2002**

CASE AUTH/1287/3/02

MERCK SHARP & DOHME v PROCTER & GAMBLE

Didronel PMO mailing

Merck Sharp & Dohme complained about a GP mailing for Didronel PMO (etidronate disodium and calcium carbonate) issued by Procter & Gamble. The mailing consisted of a leaflet headed 'Before prescribing your next bisphosphonate therapy take a look inside …'. The leaflet opened up and continued '… there are some important things to consider …' which appeared above a detachable laminated card headed 'Gastro-intestinal [GI] contraindications, warnings & precautions need to be considered before prescribing a bisphosphonate'. The card compared Didronel PMO with alendronate once weekly 70mg (Merck Sharp & Dohme's product Fosamax Once Weekly). The data for each medicine had been taken from the relevant section of its summary of product characteristics (SPC).

Merck Sharp & Dohme noted that comparison of the parts of the SPCs reproduced was very selective such that the card did not reflect all the evidence in the SPCs about GI issues. Parts of the SPC which related to GI issues but were less favourable to Didronel PMO had been omitted. For example the SPCs for both products contained statements regarding peptic ulcers. That for alendronate was reproduced verbatim in the laminated card 'Whilst no increased risk was observed in clinical trials, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications. A causal relationship cannot be ruled out'. The Didronel PMO SPC contained what appeared to be a more definitive statement as a GI side-effect 'Reports of exacerbation of peptic ulcer with complications in a few patients'. However, this was not reproduced in the laminated card. Therefore, Merck Sharp & Dohme believed that the card was not a fair comparison, it did not reflect all the evidence and was misleading. A further breach was alleged as the GI side-effects associated with Didronel PMO were not reflected.

Whilst the words from the GI contra-indications, warnings and precautions section were reproduced the format was not. The SPC for Fosamax Once Weekly used solid text, but in the mailing some of the words and phrases were produced as bullet points. Merck Sharp & Dohme considered that this had the dual effect of highlighting them and giving the visual impression of greater length. The comparison was alleged to be unfair as was the format.

Merck Sharp & Dohme alleged that the mailing was disparaging.

In the Panel's view most readers would assume that the laminated card gave all the information that needed to be considered with regard to GI effects. This was not so. Although it was stated that the information related to contraindications, warnings and precautions these were regulatory terms and many prescribers would not realise that GI side-effects had not been included. There was thus no mention of the statement in the Didronel PMO SPC 'In clinical studies of 2-3 years duration, the incidence of [GI] events were comparable to placebo. The most common effects reported in order of incidence were diarrhoea, nausea, flatulence, dyspepsia, abdominal pain, gastritis, constipation and vomiting. Reports of exacerbation of peptic ulcer with complications in a few patients'. It was irrelevant where the statement appeared in the SPC. The possible GI side-effects would be important when considering prescribing Didronel PMO in preference to Fosamax Once Weekly. The Panel ruled breaches of the Code as it considered that the laminated card failed to reflect all the available information and was a misleading and unfair comparison.

The information about Fosamax Once Weekly on the laminated card was consistent with the SPC although the presented form was very different. Whilst there were more statements in the Fosamax Once Weekly SPC than in the Didronel PMO SPC the use of bullet points to present the data relating to the former exaggerated the difference between the products. No bullet points had been used for the data relating to Didronel PMO. The Panel considered that the comparison was unfair and in that regard disparaged Fosamax Once Weekly. Breaches of the Code were ruled.

Merck Sharp & Dohme Limited complained about a mailing (ref EBUD003) for Didronel PMO (etidronate disodium and calcium carbonate) issued by Procter &

Gamble Pharmaceuticals UK, Limited. The mailing consisted of an A4 leaflet headed 'Before prescribing your next bisphosphonate therapy take a look inside …' which opened up and continued '… there are some important things to consider …'. This appeared above a laminated card headed 'Gastro-intestinal contraindications, warnings & precautions need to be considered before prescribing a bisphosphonate' which compared Didronel PMO with alendronate once weekly 70mg (Merck Sharp & Dohme's product Fosamax Once Weekly). The laminated card bore the prescribing information for Didronel PMO on its reverse and was designed to be separated from the leaflet. The mailing had been sent to general practitioners.

COMPLAINT

Merck Sharp & Dohme alleged that the mailing contravened the Code. Unfortunately it had not been able to reach a satisfactory conclusion with Procter & Gamble.

The laminated card enclosed with the mailing compared the gastro-intestinal (GI) contraindications, warnings and precautions for Didronel PMO and alendronate. Merck Sharp & Dohme did not believe this was a fair comparison as required by Clause 7.3 of the Code. The choice of which parts of the summaries of product characteristics (SPCs) to reproduce was very selective and other parts of the SPCs which were related to GI issues and less favourable to Didronel PMO had been omitted. Those chosen had been reformatted with listed bullets so as to make those for alendronate appear longer.

The amount of product information in SPCs varied markedly. For example the pharmacodynamic sections for Didronel PMO and Fosamax Once Weekly. There were a variety of different reasons for this, eg individual pharmaceutical companies had very different approaches to the amount of information they wished to include, impact of different regulatory procedures and guidelines, and temporal factors such as total patient exposure which influenced identified side-effects and drug interactions. All these might mean that a comparison of the same sections of two SPCs might be inappropriate.

As an example of omission and this variation, the SPCs for both products contained statements regarding peptic ulcers. That for alendronate appeared in Section 4.4 of the SPC and was reproduced verbatim in the laminated card 'Whilst no increased risk was observed in clinical trials, there have been rare (post-marketing) reports of gastric and duodenal ulcers, some severe and with complications. A causal relationship cannot be ruled out'. Section 4.8 of the Didronel PMO SPC contained what appeared to be a more definitive statement as a GI side-effect, 'Reports of exacerbation of peptic ulcer with complications in a few patients'. However, this was not reproduced in the laminated card. Therefore, Merck Sharp & Dohme believed that the card was not a fair comparison and did not reflect all the evidence in breach of Clause 7.2 and was misleading in breach of Clause 7.3. Merck Sharp & Dohme also alleged a breach of Clause 7.9 as the GI side-effects associated with Didronel PMO were not reflected. Merck Sharp & Dohme did not believe that inclusion of the statement in the prescribing information on the other side of the laminated card absolved Procter & Gamble of its obligation not to mislead in the promotional item itself.

Whilst the words from the GI contra-indications, warnings and precautions section were reproduced faithfully, the format was not. Within the SPC for Fosamax Once Weekly these were solid text, but in the mailing some of the words and phrases were produced as bullets within a table for the two products being compared. The bullets had the dual effect of highlighting them and giving the visual impression of greater length. Merck Sharp & Dohme alleged that on this basis the comparison was unfair in breach of Clauses 7.2 and 7.3, and the format breached Clause 7.8.

The lamination of the card was a contrast with the rest of the mailing and was, Merck Sharp & Dohme believed, an indication of the intention that the card should be kept for reference, rather than disposed of with the rest of the mailing. In view of this Merck Sharp & Dohme had requested Procter & Gamble to send a corrective mailing to recipients of the mailing, but it had declined to do so. In reviewing the case Merck Sharp & Dohme asked the Authority to consider the possibility of a corrective mailing in its judgement.

Given the unfairness of the comparison, the reformatting of the text so as to make it appear longer and highlight certain words or phrases, and the laminating of the card, Merck Sharp & Dohme alleged that the mailing was disparaging and constituted a breach of Clause 8.1.

In summary Merck Sharp & Dohme considered that the mailing was unfair and disparaging in breach of Clauses 7.2, 7.3, 7.8 and 8.1, and provided an inaccurate impression of GI safety for Didronel PMO in breach of Clause 7.9.

RESPONSE

Procter & Gamble noted that Merck Sharp & Dohme argued that a comparison of the same sections of two product SPCs might be inappropriate. However, Procter & Gamble believed that as an independent, expert-reviewed summary of the product, the SPC could be seen as perhaps the best basis for a comparison, if no independent, appropriate and unbiased head-to-head comparative study of two products existed.

Didronel PMO GI side-effects – including peptic ulcer – were not included in this mailing because it compared only one material, relevant, substantiable and representative feature, in line with Clause 7.3. The only feature compared was contraindications, precautions and warnings related to the GI tract. This area was clearly very relevant to the prescribing decision, was substantiable based on the approved product labelling, and was by definition representative because it was the information chosen by regulatory authorities to include in these sections

of the SPC for the product based on all the clinical and post-marketing data available. Further, Procter & Gamble believed that this information was fair and balanced, in line with Clause 7.2, and reflected the available evidence because the same information was provided for each product, taken directly from the up-to-date version of each approved SPC (October 2000 and November 2000 respectively). In previous correspondence with Merck Sharp & Dohme, Procter & Gamble had made it clear that it had no objection to enclosing the full SPC for Didronel PMO in a future mailer for its product, but Merck Sharp & Dohme had not commented on this proposal.

There were indeed a variety of different reasons why the amount of information in SPCs varied. However, contraindications, precautions and warnings and the information contained within these sections were influenced by the available data (from clinical trials and post-marketing surveillance) and by guidance from the regulatory authorities, rather than the 'wishes' of the company. Procter & Gamble agreed that temporal factors such as total patient exposure were important, but surely this would tend to increase the information in an SPC rather than decrease it, as it provided information on 'real life' usage of the product which might not be apparent in clinical trials. Didronel PMO had been on the market in the UK for 10 years, with more than one million patient-years of exposure. Although Didronel PMO was first licensed in 1991, it was important to note that the product underwent a thorough review in September 1996 when the data sheet was updated into an SPC. Thus there was no basis to believe that the SPC was any way less 'complete' than that for Fosamax.

The regulatory authorities requested information to be presented in certain sections depending on the information available and the prominence with which it needed to be mentioned. A statement concerning gastric and duodenal ulcers had been required by the Medicines Control Agency (MCA) in the precautions and warnings section of the Fosamax Once Weekly SPC. In contrast, a statement concerning peptic ulcers had not been required by the MCA in the precautions and warnings section of the Didronel PMO SPC. The MCA required periodic safety updates as part of post-marketing safety monitoring for any medicine. The most recent of these for Didronel PMO was provided in December 2001. If the post-marketing surveillance data that Procter & Gamble had supplied had required additional GI contraindications, precautions and warnings, or other changes to the SPC, the MCA would have advised Procter & Gamble of this as it had done in the past with Didronel PMO and other products. The single GI precaution for Didronel PMO was increased frequency of bowel movements in chronic diarrhoeal disease or enterocolitis, as stated in the mailing. Procter & Gamble re-iterated that Clause 7.9 was not relevant as it was not comparing on side-effects, nor did the current material state that Didronel PMO was safe or free from side-effects.

The text from the contraindications, precautions and warnings sections of the SPCs was formatted in exactly the same way for each product. Procter & Gamble believed that this complied with Clause 7.8. The horizontal distance from each bullet point to the end of the longest line of text was the same (8.7 cm). Any possible format would give 'the visual impression of greater length' because there was much more text in these sections for Fosamax Once Weekly than for Didronel PMO.

Again, Procter & Gamble disagreed that the information included in this mailer was disparaging in breach of Clause 8.1 for the reasons given above and because the information was taken directly from the SPC.

Merck Sharp & Dohme had stated in its complaint that it had 'not been able to reach a satisfactory conclusion with Procter & Gamble'. However, Merck Sharp & Dohme's complaint to the Authority raised several points and alleged breaches of clauses that it had not raised with Procter & Gamble, and which could perhaps have been settled without recourse to the Panel.

PANEL RULING

The laminated card was headed 'Gastro-intestinal contraindications, warnings and precautions need to be considered before prescribing a bisphosphate'. In the Panel's view most readers would assume that the card gave all of the information that needed to be considered with regard to GI effects. This was not so. Although it was stated that the information related to contraindications, warnings and precautions these were regulatory terms and many prescribers would not realise that GI side-effects had not been included. There was thus no mention of the statement in the Didronel PMO SPC 'In clinical studies of 2-3 years duration, the incidence of [GI] events were comparable to placebo. The most common effects reported in order of incidence were diarrhoea, nausea, flatulence, dyspepsia, abdominal pain. gastritis, constipation and vomiting. Reports of exacerbation of peptic ulcer with complications in a few patients'. The Panel considered that it was irrelevant where the statement appeared in the SPC. The possible GI side-effects would be important when considering prescribing Didronel PMO in preference to Fosamax Once Weekly. The Panel considered that the laminated card was not a fair reflection of the evidence and was a misleading and unfair comparison. The Panel ruled breaches of Clauses 7.2 and 7.3. The laminated card failed to reflect all the available information and a breach of Clause 7.9 was ruled as alleged.

With regard to the format and presentation of the information the Panel noted that the information about alendronate once weekly on the laminated card was consistent with the SPC although the way in which it had been presented was very different. Although there were more statements in the Fosamax Once Weekly SPC than in the Didronel PMO SPC the use of bullet points to present the data relating to alendronate once weekly exaggerated the difference between the products. No bullet points had been used for the data relating to Didronel PMO. The Panel considered that the comparison was unfair and in that regard disparaged Fosamax Once Weekly. Breaches of Clauses 7.2, 7.3, 7.8 and 8.1 of the Code were ruled as alleged.

The Panel noted Merck Sharp & Dohme's request that the Authority consider the possibility of requiring a corrective mailing. The Panel could not require that a corrective statement be issued. In accordance with Paragraph 12.2 of the Constitution and Procedure only the ABPI Board of Management could require a company to issue a corrective statement. The Panel did not consider that the case warranted a report to the Appeal Board for it to consider whether to report the matter to the ABPI Board of Management.

Complaint received **13 March 2002**

Case completed **15 May 2002**

CASE AUTH/1289/3/02

MEDICAL DIRECTOR OF AN AMBULANCE SERVICE NHS TRUST v ROCHE

Promotion of Rapilysin

The medical director to an ambulance service NHS trust complained about a meeting with a medical adviser, an area manager and a representative of Roche to discuss the use of thrombolytics by ambulance personnel in patients with acute myocardial infarction. Roche supplied Rapilysin (reteplase).

The complainant stated that in the meeting the medical adviser rubbished tenecteplase, the thrombolytic chosen for use in the trust. He produced old papers relating tenecteplase performance to TPA [alteplase] and claimed that one of the problems was the ability of paramedics to judge body weight, claiming that this had been the case in another ambulance service. The complainant had subsequently spoken to the medical director of that service and found out that this was not the case.

The complainant was sad that such a respected company should choose to give her only partial information from selected trials as well as telling her of decisions taken by other trusts, which were misleading.

The complainant confirmed that she had met previously with the representative and that it was the representative who requested that the medical adviser also came to see her. The complainant had explained that a decision had been made to use tenecteplase, but the representative still thought the visit would be useful. The complainant stated that she agreed to the visit to expand her knowledge.

The complainant noted that the main issue raised was that paramedics could not judge patients' weights. The ability to guess weights was not seen as a problem, and was tested on five paramedics within the trust who were to pilot the use of tenecteplase. A small error of judgement was considered an acceptable risk in view of the benefit gained and this was supported by several papers. The complainant stated that she had read the relevant papers relating to thrombolysis. The complainant took exception to the comments that the local ambulance service's decision to use tenecteplase might not have taken account of the risk of errors in weight-based dosing regimes.

The Panel noted that the parties' accounts of what took place differed. The Panel noted that the ambulance service NHS trust in question had already made the decision to use tenecteplase in acute myocardial infarction. During their discussions with the complainant the representatives had referred to the need to administer tenecteplase on the basis of body weight. The summary of product characteristics (SPC) for tenecteplase (Boehringer Ingelheim's product Metalyse) gave a dosage scheme such that the correct volume and dose of the product, according to a patient's body weight, could be calculated. Conversely the SPC for Rapilyse made no reference to weight-adjusted dosing. In the Panel's view it was neither disparaging for Roche's representatives to refer to this difference nor misleading; no breaches of the Code were ruled.

The Panel noted that the complainant had considered that her professional competence had been questioned. The Panel noted Roche's submission that its medical adviser wished to point out that the decision to use tenecteplase might have been precipitate, given that there was an alternative that had not been previously considered. In this regard the Panel considered that on balance high standards had not been maintained and ruled a breach of the Code.

The Panel did not consider that the matter was one which brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 of the Code was ruled in this respect.

The medical director to an ambulance service NHS trust, complained about a meeting with representatives of Roche Products Limited to discuss thrombolytics for use by ambulance personnel in patients with acute myocardial infarction (AMI) prior to their hospital admission. Roche supplied Rapilysin (reteplase).

COMPLAINT

The complainant was visited by a medical adviser, an area manager and a representative. The complainant had met the representative before who had asked the complainant if he might bring the medical adviser to discuss Roche's thrombolytics.

The complainant stated that the first ten minutes of the meeting were taken up with the medical adviser

rubbishing tenecteplase, the thrombolytic chosen for use in her trust. He produced one or two old papers and was relating tenecteplase performance to TPA [alteplase] and also claiming that one of the problems was the ability of paramedics to judge body weight, claiming that this had been the case in another ambulance service. The complainant had subsequently spoken to its medical director and this was not the case. The complainant felt the Code had stopped this type of behaviour and she was particularly concerned as this was a reputable company. The complainant stated that she would not be seeing representatives from Roche in future. The complainant knew that the representative was very concerned about this visit as she had made it clear that she did not expect doctors to behave in this way.

When writing to Roche the Authority drew attention to Clauses 2, 7.2, 8.1, 9.1, 15.2 and 15.9 of the Code.

RESPONSE

Roche stated that the representative was senior healthcare programmes manager in Roche's health care management department. This department was concerned with NHS strategic issues, eg NICE submissions and health economics. As such, it was not involved in sales or promotion and the senior healthcare programmes manager was not required to pass the ABPI representatives examination. He had visited the complainant to brief her on the NHS budget impact model that was used in Roche's NICE submission for Rapilysin.

The meeting in question had been arranged following this preliminary meeting. The complainant had indicated that she would like to hear more about Rapilysin and agreed to meet a medical adviser.

Roche did not accept any breach of the Code and submitted that the meeting should be seen within the context of a recent development in the treatment of AMI. Research had shown, and it was widely accepted, that AMI should be treated with thrombolytics as soon as possible in order to limit myocardial damage and to improve outcome. Usually thrombolysis was initiated in hospital but there were now moves to use the ambulance service to treat the patient prior to hospital admission (ie pre-hospital thrombolysis). Clearly there was a need for accurate diagnosis and simple easily administered thrombolytic regimens as these medicines were given intravenously and had the potential for serious adverse reactions eg cerebral haemorrhage. Currently very few ambulance services used pre-thrombolysis in AMI.

Some of the current thrombolytics had dose regimens tailored to individual characteristics such as weight. In the past, thrombolytics were given as an infusion or a single bolus dose followed by continuous infusion over 60 mins. Whereas this was practicable in the hospital setting, it would be cumbersome in the pre-hospital situation. An added complication was the necessity to precede the thrombolytic infusion with a heparin bolus that needed to be adjusted for weight.

In the pre-hospital setting, therefore, health professionals were likely to choose the thrombolytic with the most convenient, simple and safe method of administration. Two thrombolytics were of particular value in this regard. Rapilysin was administered as two bolus injections separated by 30 minutes. Neither the dosage of Rapilysin nor the initial heparin bolus needed to be adjusted for age or weight, and the heparin infusion that followed Rapilysin only needed to be started after the second bolus. The other thrombolytic (tenecteplase), marketed by another company, was given as a single bolus injection, but its dose and that of the initial heparin administration needed to be weight-adjusted in order to achieve optimal coronary reperfusion. Also, the heparin infusion needed to be started after the initial tenecteplase bolus.

There were thus advantages and disadvantages for both thrombolytics although both were more suitable than other existing agents for the pre-hospital setting. Both companies promoted their product in this area and currently many NHS regions were considering implementing pre-hospital thrombolysis and deciding on the optimum product. As this was a complex area it was important that all the evidence was evaluated before any final decision was taken on which medicine to use.

The disadvantage of using tenecteplase was the additional requirement to weigh the patient in order to be sure of the dose. A recent paper on the risk from medication errors for various thrombolytics showed the importance of correct weight adjustment for limiting serious bleeding complications (Cannon 2000). In addition, data from the TIMI 10B trial showed that at the higher dosing range there was substantial increase in haemorrhagic risk and mortality (Cannon *et al* 1998). Cannon stated in relation to tenecteplase that 'serious bleeding also increased from 4.5% for those receiving the optimal dose to 12% for patients receiving too high a dose'.

This was the background to the meeting. The Roche representatives were aware that a decision had already been taken by the local ambulance service to use the competitor product. They adopted the view therefore that one could not discuss the one product in isolation and Roche accepted that the discussion initially concentrated on whether the decision about the competitor's product had taken account of the risks of errors in weight-based dosing regimens. The results of the above papers were used to illustrate this.

The complainant interrupted during this initial discussion to say she was uncomfortable about this approach and the group apologised and moved the conversation on to provide details of the international trials of Rapilysin in the pre-hospital setting.

Roche did not accept that the competitor's product had been 'rubbished' as the arguments were based on sound data and publications. In addition, these were not old papers but highly relevant articles from peer review journals. Moreover, Cannon was a leading authority on thrombolytic trials.

Similar discussions had taken place with other ambulance services, cardiologists and other decision makers without complaints. Indeed, on many occasions, the decision makers had not been aware of

the implications of the need for weight-based dosing nor of the published risks of dosing errors.

On the question of what was said about other ambulance services, the recollection of Roche's regional sales manager was that he named two ambulance services currently using Rapilysin in a pre-hospital setting. He was also aware that another ambulance service was due to make a decision regarding choice of pre-hospital thrombolytic. He stated that although he did not know the outcome of this decision the lead physician from one of the hospitals had just verbally agreed to convert to Rapilysin in the hospital setting.

Roche submitted that the information on Rapilysin and tenecteplase provided by the medical adviser was fair and accurate. This was a complex therapeutic area. Because of this the company had provided a physician who was experienced in treating AMI and had studied the literature extensively on the use of thrombolytics. He did not produce old papers but discussed relevant peer reviewed pertinent ones. Nor did he imply that tenecteplase 'performance related to TPA' but pointed out using recent (not old) papers that tenecteplase and other thrombolytics could be problematic when medication errors were made. It was self-evident that medication errors were possible if the estimation of the patient's weight was not accurate, particularly at the higher dose range.

The information about the other local ambulance service did not make reference to its ability to judge body weight but that these same issues had been discussed with this service, and a decision on which thrombolytic to use pre-hospital had yet to be made. The statement about the use of Rapilysin as pre-thrombolysis in the other two ambulance services Roche could confirm was true.

However the medical adviser in question was relatively new to the industry and had relatively little experience in discussing these types of issues with doctors in the context of contracts, etc, particularly in this case where a decision had already been taken. It was possible that the manner of the presentation resulted in the discomfort of the complainant, particularly if the implications of the weight-based dosing had not been appreciated when the decision had been made prior to the meeting but this, Roche submitted, was a subjective situation. It was pertinent to the case that the complainant stated that ambulances could be provided with machines to measure weight in view of this information, something that might not have previously been considered. Thus, although Roche regretted that such a discussion between two doctors led to a complaint it did not accept a breach of the Code.

In any discussion about the use of pre-hospital thrombolysis it was inevitable that the two main products were discussed, the one in relation to the other. In this situation, because a decision to use the competitor product had already been taken it was felt appropriate to point out the disadvantages of this product versus Rapilysin. The Roche representatives present presumed that the benefits of the competitor product were well known to the complainant as it had been chosen by the trust.

Two main points were made. The competitor's product required weight-based dosing. This was not a trivial requirement, as detailed above. In addition, the apparent advantage of a single bolus dose was somewhat reduced by the need for heparin infusion. These were 'evidence-based' statements about the product. There was no intention to disparage the product nor did anything that was said actually 'rubbish' the product. Bearing in mind that this was a life threatening condition and a major public health concern that was being debated, it was understandable that Roche's medical adviser wished to make these points. Therefore a breach of Clause 8.1 was denied.

The special nature of medicines and the professional standing of the audience was indeed recognised in this situation where it was felt the discussion should be led by the medical adviser for this disease area rather than a sales or marketing representative. It was possible that the medical adviser put the case in a robust way, which was uncomfortable for the complainant, particularly as evidence was produced that might not have previously been considered. Perhaps the structure of the discussion could have been different but as soon as the complainant indicated her discomfort the group apologised and moved on. Roche submitted also that there was a misunderstanding about what was said about other ambulance services.

Roche therefore did not accept a breach of Clause 9.1.

The company submitted that the representatives did comply with the need for high standards. The company accepted that there could be misunderstandings and subjective discomfort with the way data was presented but that this did not constitute a breach of Clause 15.2 of the Code.

The company had briefing material for representatives on Rapilysin. However, on this occasion, the company considered that because of the nature of the discussion and the importance of the audience, the company cardiovascular expert , namely the medical adviser, should present the data. It was normal practice in the industry for medical to medical discussions, which were usually more extensive and detailed than the briefing details for the sales representatives. Again Roche did not accept that a breach of Clause 15.9 of the Code occurred.

In summary, the company regretted that this meeting resulted in a complaint (without accepting a breach had taken place), particularly as this was the result of an important meeting mainly between two medically qualified people. The company submitted that the data presented were robust, relevant and should be considered carefully by physicians responsible for this relatively new situation of pre-hospital thrombolysis.

The medical adviser was aware that this particular ambulance service had made a decision about the use of a competitor product yet now wished to hear about an alternative. He wished to point out data that showed that the decision might have been precipitate, given that there was an alternative that had not previously been considered. The data and evidence were robust and relevant and based on an up-to-date search of the literature and the details of both

summaries of product characteristics (SPCs). There was no intention to disparage a competitor's product, nor was false information given about decisions at other ambulance services. The company had investigated this thoroughly with the representatives and was satisfied that false information was not given about other ambulance services. It was possible that misunderstandings could have occurred in relation to use of Rapilysin in hospital and pre-hospital settings.

The company had also investigated this case on the basis that perhaps the evidence was presented in too enthusiastic or robust a manner by someone new to the industry and not experienced in this type of interview. However, if this were so, it had more to do with experience, style and technique. However, the other Roche representatives present did not feel this was the case.

Nonetheless, the company regretted that the meeting led to a complaint and it was not the company's intention to alienate the profession. Roche did not accept breaches of the Code and therefore did not feel that this had brought the industry into disrepute (Clause 2).

With Roche's agreement its response was sent to the complainant for comment.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that the basis of her complaint was about the manner in which the visit took place, with the concentration on denigrating tenecteplase rather than telling her about Rapilysin. The complainant was also sad that such a respected company should choose to give her only partial information from selected trials as well as telling her of decisions taken by other trusts, which were misleading. However, she was not sure she was able to rehearse the scientific arguments to refute this in so expert a manner as Roche had done.

The complainant confirmed that she had met with the senior healthcare programmes manager to discuss the NHS budget impact, which she found very interesting, but it was he who requested he bring his medical adviser to see her, despite her suggesting it might be a waste of time. The complainant had mentioned that she had seen the medical adviser at the first NICE Technologic Appraisal meeting but had not had a chance to talk with him. She had explained that a decision had been made to use tenecteplase, but the senior healthcare programmes manager still thought the visit would be useful. The complainant stated that she thus agreed to the visit both to expand her knowledge and to please a colleague.

The complainant noted that the main issue raised was around the safety of tenecteplase, in that paramedics could not judge patients' weights. The ability to guess weights was not seen as a problem, and was tested on five paramedics within the trust who were to pilot the use of tenecteplase. A small error of judgement was considered an acceptable risk in view of the benefit gained. This was supported by the work by Brad Angeja *et al* (2001) which showed an acceptable margin of safety with errors in weight-adjusted dosing of tenecteplase. Indeed, the author Cannon, quoted by Roche, also produced a paper where he showed that guessing weights in accident and emergency departments prior to thrombolytic administration was pretty accurate and where there were errors of weight estimate, there was no difference in mortality or intercranial haemorrhage. Both TIMI 10B and ASSENT-1 supported this.

The complainant noted that Roche's response went on to comment on the need for a heparin infusion, but the complainant's trust was going to use a recognised regime of a single bolus heparin injection, with the infusion being started in hospital as it did not have very long journeys. Weight adjustment was required but was thought to be required for all heparin accompanying a thrombolytic.

The complainant stated that she had read the relevant papers relating to thrombolysis, and had taken advice from colleagues. She therefore took exception to the comments that the local ambulance service's decision to use tenecteplase might not have taken account of the risk of errors in weight-based dosing regimes.

The complainant stated that she was totally perplexed by the comments regarding ambulances being provided with machines to measure weight. There was no mention of ambulances being equipped with weighing facilities and again there was an implication that the trust had not considered weight-related dosing. There was certainly no 'discomfort of the complainant' but there was some increasing irritation at these slurs on her competence. This theme recurred yet again in Roche's consideration of Clauses 9.1 and 15.2 and in the company's summary where there was an inference that the trust's decision might have been precipitate!

PANEL RULING

The Panel noted that the parties' accounts of what took place when the representatives visited the complainant differed. The Panel observed that it was difficult in such cases to know exactly what had transpired between the parties. A judgement had to be made on the evidence which was available, bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint.

The Panel noted that the ambulance service NHS trust in question had already made the decision to use tenecteplase in AMI. The complainant stated that she agreed to the meeting with the representatives of Roche, however, to expand her knowledge and also to please a former colleague who now worked for the company. During their discussions with the complainant the representatives had referred to the need to administer tenecteplase on the basis of body weight. The SPC for tenecteplase (Boehringer Ingelheim's product Metalyse) gave a dosage scheme such that the correct volume and dose of the product, according to a patient's body weight, could be calculated. Conversely the SPC for Rapilyse made no reference to weight-adjusted dosing. A standard 10U bolus dose was given followed by a second 10U bolus dose 30 minutes later. The supplementary information to Clause 8.1, Disparaging References, noted that much pharmaceutical advertising

contained comparisons with other products and, by the nature of advertising, such comparisons were usually made to show an advantage of the advertised product over its comparator. Provided that such critical references to another company's products were accurate, balanced, fair etc, and could be substantiated, they were acceptable under the Code. With regard to the need for weight-adjusted dosage, tenecteplase and Rapilysin clearly differed; such adjustment for tenecteplase was required but was not needed for Rapilysin. In the Panel's view it was neither disparaging for Roche's representatives to refer to this difference nor misleading; no breaches of Clauses 8.1 and 7.2 were ruled. Although the complainant had referred to work which demonstrated an acceptable margin of safety in errors in weight-adjusted doses the Panel noted that claims and comparisons etc must not be inconsistent with the particulars listed in a product's SPC.

The Panel noted that the complainant had considered that her professional competence had been questioned in that perhaps she had not fully appreciated the need for weight-adjusted dosing before choosing tenecteplase for the ambulance service NHS trust. The Panel noted Roche's submission that the medical adviser wished to point out data to the complainant that showed that the decision to use tenecteplase might have been precipitate, given that there was an alternative that had not been previously considered. In this regard the Panel considered that on balance high standards had not been maintained and ruled a breach of Clause 9.1. The Panel considered that the provisions of Clause 15.2 were covered by this ruling.

The Panel did not consider that the matter was one which brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

The Director noted that the meeting was a one off principally between the complainant and Roche's medical adviser. In the circumstances the Director did not consider that the medical adviser needed briefing material as described in Clause 15.9 of the Code and decided that there was thus no *prima facie* case to answer under the Code in that regard.

Complaint received **20 March 2002**

Case completed **15 May 2002**

CASE AUTH/1291/3/02

PFIZER v LILLY

Promotion of tadalafil at an international meeting

Pfizer alleged that at the recent Congress of the European Association of Urology in Birmingham, Lilly had promoted tadalafil prior to the grant of its marketing authorization.

Pfizer noted that nowhere on a stand, jointly organised by Lilly and ICOS, was it mentioned that tadalafil did not have a UK marketing authorization. The stand was highly coloured including pictures of couples and quotes of a promotional nature. Basic specificity and pharmacokinetic data were presented, along with a ring-bound folder containing clinical posters. A statement declaring that tadalafil was 'under investigation for the treatment of sexual dysfunction' and a small footnote on certain panels stating that tadalafil was 'strictly limited to ongoing trials by qualified investigators', did not in any way excuse such promotional activity. Lilly had confirmed that at least some of the materials were not certified in accordance with the Code.

The Panel noted that, at the time of the meeting in question, tadalafil was not licensed anywhere in the world. An application for a UK marketing authorization had been made.

In the Panel's view it was not unacceptable for Lilly to provide the delegates at the meeting with information about tadalafil. Any material provided, however, given that tadalafil was not licensed anywhere in the world, had to be restricted to the exchange of medical and scientific information; it must not be promotional either in tone or content.

A panel, which appeared to be situated behind the 'front desk' of the stand in question, stated, *inter alia*, that 'Currently Lilly ICOS is developing tadalafil, an oral [phosphodiesterase type 5] inhibitor under investigation for the treatment of sexual dysfunction'. A series of black and white panels on the stand used quotations from patients or partners to explain the impact that erectile dysfunction had on their lives, and there were four full colour panels showing couples. A further four panels gave details of factors affecting the pharmacokinetics of tadalafil and at the bottom of each it stated 'Caution: Use of this product is strictly limited to ongoing clinical trials by qualified investigators'. Also available at the stand was a computer kiosk. The computer programme gave further information about Lilly and ICOS in addition to topics related to erectile dysfunction. Slides depicting a selection of the tadalafil clinical trial data were available for viewing. Delegates could view, and request, a copy of an erectile dysfunction slide kit which gave general information about the condition, but made no reference to tadalafil. An abstract booklet with the results from various trials on tadalafil was presented in the style of scientific posters.

In the Panel's view, while the information provided on the stand could have been regarded as the legitimate exchange of medical and scientific information, the way in which it was provided and the impression created was important. The panel behind the front desk introduced delegates to tadalafil and stated that it was under investigation for the treatment of sexual dysfunction; four other panels, each with tadalafil in their headings, gave details about the product. The Panel considered that notwithstanding the fact that each of these panels stated that tadalafil was still under investigation, actively bringing the product to the attention of delegates in this way was in effect promoting it prior to the grant of a marketing authorization. A breach of the Code was ruled.

Pfizer Limited alleged that Eli Lilly and Company Limited was promoting tadalafil prior to the grant of its marketing authorization.

COMPLAINT

Pfizer stated that at the recent Congress of the European Association of Urology, held in Birmingham, there was a stand in the exhibitors' hall organised jointly between Lilly and ICOS. This stand consisted primarily of several panels of information on the recently developed product tadalafil, along with screens displaying quotes from various countries from a survey on certain aspects of sexual activity. Pfizer's view was that the content of the stand did not comply with the Code.

A letter outlining concerns over the stand material and requesting a prompt explanation was sent to Lilly. The reply confirmed that at least some of the materials were not certified in accordance with Clause 14, as stated in the supplementary information to Clause 3.

Tadalafil did not at present have a UK marketing authorization (or in fact any such authorization worldwide, as far as Pfizer was aware), and was the primary product on display at the stand. The stand was highly coloured in a promotional style, and also included at least two highly coloured pictures of couples, and quotes which when taken in light of the primary product on the stand were of a highly promotional nature. Photographs of the stand were provided.

Nowhere on the stand was it mentioned that tadalafil did not have a UK marketing authorization. Basic specificity and pharmacokinetic data were presented, along with a ring-bound folder containing clinical posters. A statement declaring that tadalafil was 'under investigation for the treatment of sexual dysfunction' and a small footnote on certain panels stating that tadalafil was 'strictly limited to ongoing trials by qualified investigators', did not in any way excuse such promotional activity.

Pfizer alleged a breach of Clause 3.1 of the Code.

RESPONSE

Lilly stated that tadalafil was not currently licensed anywhere in the world. The UK marketing authorization had been applied for.

For the purposes of bringing tadalafil to market, Eli Lilly and Company had entered into a joint venture agreement with a company called ICOS LLC (based in Seattle, USA).

Lilly reviewed proposed material for the stand with a view to sharing legitimate scientific information. It subsequently rejected some of this material as being inappropriate. The final material was not submitted and as such the final layout and juxtaposition of the stand panels was not seen prior to their production (in the USA), shipping and erection at the conference. Items previously rejected, and in particular the inclusion of the phase 3 abstract book, were present on the stand against the UK company's recommendations.

It was with the deepest apology that Lilly admitted that the materials displayed at the conference were not in accordance with the recommendations laid out by the Code. It was recognised that Lilly in the UK was accountable for the actions of other parts of the organisation when they took part in UK based activities. Lilly in the UK had told its US based colleagues that such a scenario should not occur again and it had had significant input to a Lilly Global Standard Operating Procedure. This gave clear guidance that all materials should be subject to the formalised affiliate approval process.

PANEL RULING

The Panel noted that the stand in question had not been devised by Lilly in the UK; it had been put together in the States. Nonetheless it was an established principle under the Code that UK companies were responsible for activities undertaken in the UK which promoted the prescription, sale, supply or administration of their medicines even when undertaken by the overseas head office. As acknowledged by Lilly, it was thus responsible under the Code for the stand.

The Panel noted that, at the time of the meeting in question, tadalafil was not licensed anywhere in the world; an application had been made for a UK marketing authorization. Clause 3.1 of the Code stated that a medicine must not be promoted prior to the grant of a marketing authorization which permitted its sale or supply. Supplementary information to Clause 3, Marketing Authorization, stated that the legitimate exchange of medical and scientific information during the development of a medicine was not prohibited provided that any such information or activity did not constitute promotion which was prohibited under Clause 3 or any other clause.

The meeting at which the alleged promotion of tadalafil occurred was the Congress of the European Association of Urology held in Birmingham. Further supplementary information to Clause 3, Promotion at International Meetings, stated that the display and provision of promotional materials for medicines which did not have a UK marketing authorization but which were so authorized in another major industrialised country was permitted at international meetings in the UK provided that certain conditions were met. The Panel noted however that as tadalafil

was not licensed anywhere in the world, Lilly could not take the benefit of this supplementary information.

In the Panel's view it was not unacceptable for Lilly to provide the delegates at the meeting with information about tadalafil. Any material provided, however, given that tadalafil was not licensed anywhere in the world, had to be restricted to the exchange of medical and scientific information; it must not be promotional either in tone or content.

A panel, which appeared to be situated behind the 'front desk' of the stand in question explained the connection between Eli Lilly and Company and ICOS Corporation. It was stated, *inter alia*, that 'Currently Lilly ICOS is developing tadalafil, an oral [phosphodiesterase type 5] inhibitor under investigation for the treatment of sexual dysfunction'. A series of black and white panels on the stand used quotations from patients or partners to explain the impact that erectile dysfunction had on their lives. There were four full colour panels showing couples. A further four panels gave the details of the structure, selectivity, pharmacokinetics, and extrinsic factors affecting the pharmacokinetics of tadalafil. Small print at the bottom of each of these panels stated 'Caution: Use of this product is strictly limited to ongoing clinical trials by qualified investigators'. Also available at the stand was a computer kiosk. The computer programme which delegates could work through gave further information about Eli Lilly and Company and the ICOS Corporation in addition to a wide range of topics related to erectile dysfunction. Delegates were also able to view slides depicting a selection of the tadalafil clinical trial data; delegates were only able to view these slides, they could not request that they be mailed to them in any format. Delegates could however view, and request, a copy of an erectile dysfunction slide kit. These slides gave general information about the condition, its epidemiology, aetiology, diagnosis and treatment but made no reference to tadalafil. An abstract booklet had also been provided on the stand with the results from various trials on tadalafil presented in the style of scientific posters. The stand was to be looked after by four or five Lilly staff at a time. Most of these were from marketing, a few were from medical.

In the Panel's view, while the information provided on the stand could have been regarded as the legitimate exchange of medical and scientific information, the way in which it was provided and the impression created was important. The introductory panel behind the 'front desk' 'introduced' delegates to tadalafil and stated that it was under investigation for the treatment of sexual dysfunction; four other panels, each with tadalafil in their headings, gave details about the structure, selectivity and pharmacokinetics of the product. The Panel considered that notwithstanding the fact that each of these panels stated that tadalafil was still under investigation, actively bringing the product to the attention of delegates in this way was in effect promoting it prior to the grant of a marketing authorization. A breach of Clause 3.1 was ruled.

Complaint received **26 March 2002**

Case completed **20 May 2002**

CASE AUTH/1292/3/02

ASTRAZENECA v TRINITY

Promotion of Pulvinal inhalers

AstraZeneca complained about a journal advertisement, detail aid and 'Dear Colleague' letter about Pulvinal dry powder inhalers issued by Trinity. Pulvinal inhalers delivered either salbutamol or beclometasone.

The claims 'Clearly cost effective' and 'This dry powder inhaler is not only amongst the least expensive, but also cost effective in other ways' appeared in the advertisement. AstraZeneca stated that although Pulvinal was amongst the cheapest dry powder inhalers, the cited pricing information provided no evidence to suggest that its clinical efficacy was equal or greater in comparison to all other alternatives. The summary of product characteristics (SPC) for Pulvinal did not address the issue of efficacy compared to alternative treatment options. AstraZeneca alleged that the prescriber might therefore be misled by one or both of the claims into preferentially prescribing Pulvinal on a cost effectiveness basis, the claims exaggerated the significance of the data being cited to substantiate them which was in breach of the Code. Furthermore, AstraZeneca alleged that part of the second claim '… but also cost effective in other ways' was misleading; without clarification as to what these 'other ways' were the claim was ambiguous in breach of the Code.

The Panel noted that although the advertisement featured a photograph of someone holding a Pulvinal Beclometasone Dipropionate device, the text beneath the photograph referred to 'This dry powder inhaler range …'. Adjacent to the product logo 'Pulvinal Salbutamol Pulvinal Beclometasone Dipropionate' appeared beneath a depiction of each device. In the Panel's view, the claims made in the advertisement had thus to be applicable to both presentations of Pulvinal.

Part of the claim 'This dry powder inhaler range is not only amongst the least expensive …' was referenced to MIMS. No reference was given for the rest of the claim '… but also cost effective in other ways …'. In the Panel's view the term cost effective implied more than just a simple comparison of the acquisition cost of products; other factors had to be considered. Trinity had submitted a number of clinical papers to demonstrate that Pulvinal Beclometasone Dipropionate was as effective and well tolerated as other beclometasone devices and a budesonide turbohaler, in the treatment of stable moderate asthma. No similar comparative studies for Pulvinal Salbutamol had been submitted. The advertisement applied to both presentations of Pulvinal. The Panel considered that the claim 'Clearly cost effective' was misleading and exaggerated the significance of the data as alleged. A breach of the Code was ruled.

The Panel noted Trinity's submission that, apart from cost, one of the other ways in which Pulvinal inhalers were cost effective was that patients did not need to stockpile them for fear of running out as they had a transparent reservoir so it was easy to see how much powder was left. In addition Trinity had submitted that the transparency meant that patients would not discard an inhaler that was still active or inhale from one which was in fact empty. Trinity, however, had not submitted any evidence to support these potential benefits. The Panel thus considered that the claim that Pulvinal inhalers were 'cost effective in other ways' had not been substantiated and was ambiguous as alleged. A breach of the Code was ruled.

AstraZeneca noted that the claim 'Clearly asthma therapy should be simple' appeared as the heading to page 2 of the detail aid which featured four bullet points describing problems that asthma patients apparently faced. An image of a Pulvinal inhaler, directly under this list, invited the reader to assume that Pulvinal would address the problems. In the absence of supporting evidence this was inaccurate and misleading. Furthermore the image of the Pulvinal device next to a quotation from the BTS Guidelines 'Before altering a treatment step ensure that the patient is having the treatment and has a good inhaler technique', implied that the Pulvinal inhaler addressed this issue without any supporting evidence. AstraZeneca alleged that the overall impression conveyed was inaccurate and misleading and in breach of the Code.

AstraZeneca noted that the study (Johnson *et al*) upon which the claim 'Many patients are unable to generate optimum flow through a turbo inhaler' was based, was not one in which the Pulvinal device was directly compared with the Turbohaler. However within the context of the layout of this page the claim could imply to the reader that patients using the Pulvinal device would be able to generate optimal flow rate easier than if using the Turbohaler. In the absence of conclusive data the resulting impression conveyed was inaccurate and likely to mislead.

Optimal inspiratory flow rate (IFR) for the Turbohaler was 60L/min for which 30% of the nominated dose was delivered to the lungs and at an IFR of 30L/min, 15% of the dose was delivered. In contrast, the optimal IFR for Pulvinal had yet to be determined in similar studies. However there was limited *in vivo* deposition data, which showed that the Pulvinal device delivered between 11.7% and 14.15% at flow rates of 27.8L/min and 40L/min respectively. Although this evidence was not in the form of comparative *in vivo* deposition in the same study, the balance of this clinically relevant data clearly contradicted the intended message. AstraZeneca alleged that the claim was unfair and misleading and disparaged the Turbohaler device in breach of the Code.

The Panel considered that the page made no direct claims for Pulvinal. The inclusion of the photograph of a Pulvinal device and the heading 'Clearly asthma therapy should be simple', however, implied that Pulvinal would overcome the difficulties listed in the four bullet points, thus making asthma therapy simple. No data had been submitted to show that this was so. The Panel considered that the page gave a misleading and

inaccurate impression of the benefits of Pulvinal. A breach of the Code was ruled.

The Panel considered the statement 'Many patients are unable to generate optimum flow through a turbo inhaler' implied that many patients were able to generate optimum flow through a Pulvinal device. No data had been submitted in this regard and so the Panel considered that the claim was misleading as alleged and a breach of the Code was ruled.

The Panel noted that AstraZeneca stated that the optimum inspiratory flow rate required for a Turbohaler was 60L/min. Johnson *et al* showed that in a group of 15 patients, routinely using a Turbohaler, only 3 achieved a flow rate of ≥60L/min when using a teaching device consisting of a flow meter and a Turbohaler. In a group of 117 patients who were Turbohaler naïve and after they had received training only 12 achieved this flow rate. On the evidence before it, the Panel thus did not consider that it was disparaging to state that many patients were unable to generate optimum flow through a Turbohaler and no breach of the Code was ruled.

AstraZeneca noted the claim 'Clearly appeals to patients' appeared as the heading to page 4 of the detail aid followed by six bullet points which appeared to be beneficial features of the Pulvinal device. The fifth bullet point 'Significantly easier to use than a turbo inhaler' was based upon the results of a clinical study involving two groups of patients who used either the Pulvinal or the Turbohaler device to take their asthma medication (Dal Negro *et al*, data on file). Each group was assessed on how easy they found the device to use. However the study design was not cross-over so patients were unable to directly compare devices in terms of ease of use. Therefore the study was incapable of supporting this bullet point, the significance of the results being exaggerated. AstraZeneca alleged that the resulting message was misleading and in breach of the Code. AstraZeneca noted the final bullet point 'Consistent doses even at low flow rates' was referenced to two studies with the results of the only comparative study, Meakin *et al*, presented in a graph directly underneath. AstraZeneca considered that the results of this *in vitro* study had been extrapolated into the clinical situation and used to support claims around patient benefit. In the absence of appropriate clinical data to indicate the direct relevance AstraZeneca therefore believed this breached the Code. For clinical benefits, an important feature that must be considered for all devices was *in vivo* lung deposition data. The Pulvinal device delivered between 11.7% and 14.15% at flow rates of 27.8L/min and 40L/min respectively. The deposition offered by the Turbohaler had been shown to be 15% and 30% at 30L/min and 60L/min respectively and as already discussed above although this evidence was not in the form of comparative *in vivo* deposition in the same study, the balance of this clinically relevant data was in sharp contrast to the claim itself. Moreover in the context of the inhalation dynamics of an individual device, there was no evidence to support a relationship between the emitted dose and the patient benefits derived from that device. Additionally Meakin *et al* compared the emitted dose and fine particle dose (FPD) for the Pulvinal, Turbohaler and Rotohaler devices. However results for the FPD parameter were not referred to in the graph. AstraZeneca maintained that *in vitro* data should not be extrapolated to support claims around patient benefits. It was misleading to omit the FPD results, especially when they showed a variability factor of 1.6 with the Pulvinal device. Dal Negro *et al* 1997 only involved the Pulvinal device and was not a comparative study. However the high prominence in which the results of the comparative study had been presented on the page, i.e. a large graph underneath the bullet point, implied that this second study was also a comparative study against the Turbohaler (and Rotohaler). This was clearly incorrect resulting in a misleading impression to the reader. AstraZeneca alleged a breach of the Code.

AstraZeneca noted that the graph occupied almost half the page. It was important to bear in mind that this high prominence was being viewed by the prescriber in the context in which the whole was set i.e. under the title 'Clearly appeals to patients'. This gave the impression that the graph was not being used to support the individual consistency claim but the title as well. This was inaccurate and gave an overall misleading impression which AstraZeneca considered breached the Code.

The Panel noted the claim 'Significantly easier to use than a turbo inhaler' was referenced to Dal Negro *et al*, data on file which was an open, parallel group study in which 82 patients previously using a beclometasone MDI were randomised to receive either beclometasone from the Pulvinal device or budesonide from a turbo inhaler. Patient opinion of ease of use was one of the secondary efficacy variables. The Panel considered that the claim implied that patients had been able to compare both devices and found the Pulvinal device 'significantly easier to use than a turbo inhaler' which was not so. The Panel considered that the claim was thus misleading and that it had not been substantiated. Breaches of the Code were ruled.

The lower half of the page featured a graph showing the effect of flow rate on mean emitted dose delivered from a Pulvinal device, a turbo inhaler and a rota inhaler, which had been taken from Meakin *et al*, an *in vitro* study. The page heading referred to patients, and so, in the Panel's view, readers would expect that all of the data on the page would also refer to patients. The graph did not state that it was adapted from an *in vitro* study. Such data also had to be relevant to the clinical situation. The Panel considered that the presentation of the graph was thus misleading as alleged and a breach of the Code was ruled. The Panel considered that this ruling covered the allegation that the graph was not being used to support the dose consistency claims and the heading as well.

The claim 'Consistent doses even at low flow rates' was referenced to Meakin *et al* and Dal Negro *et al*. The Panel did not consider that, because data from the comparative study by Meakin *et al* had been depicted in the graph below the claim, readers

would assume that Dal Negro *et al* was also a comparative study. The claim itself did not imply a comparison with other devices and no breach of the Code was ruled, although the Panel noted its ruling above with regard to the use of *in vitro* data.

The *in vitro* study by Meakin *et al* showed that beclometasone emission from the Pulvinal device varied only slightly over the flow rate range of 28 to 63L/min which was the range of clinical interest. The fine particle dose was more sensitive to increases in flow rate, increasing by a factor of 1.6 from 22 to 35mcg. These variations were less than those observed with the Turbohaler. In their introduction the authors explained that the nature of the aerosol cloud generated from powder inhalers depended upon a complex interaction of three factors: the force of the inspiration, the design of the device, and the formulation of the powder it contained. In the Panel's view this meant that while Meakin *et al* was provided to support a claim for consistent emission of doses over a range of flow rates it applied only to Pulvinal Beclometasone Dipropionate; the results could not be assumed to apply to Pulvinal Salbutamol. The detail aid referred to both presentations of Pulvinal. The Dal Negro *et al* study did not measure the doses emitted but did show that the efficacy of salbutamol delivered via a Pulvinal device was not dependent upon generated peak inspiratory flow rate. The study measured 18 patients with moderate or severe asthma. The Panel considered that the claim was misleading and had not been substantiated and breaches of the Code were ruled.

AstraZeneca noted that the claim 'Clearly benefits you' appeared as the heading to page 5 of the detail aid; four bullet points, of which one was 'Reliable, consistent drug delivery' were featured. However this claim was based on the results of the Meakin *et al* study which, as mentioned previously, was not a drug consistency study but one which measured the relationship between IFR and % emitted dose and FPD with Pulvinal. AstraZeneca believed the data was being used out of context and was by implication inaccurate. This rendered the claim unsubstantiated and likely to mislead.

The Panel noted its comments above regarding the design of the Meakin *et al* study and its applicability to Pulvinal Salbutamol. An *in vitro* study was being used to support what would be assumed to be a clinical claim and the results from the study, which were specific to Pulvinal Beclometasone Dipropionate, were being ascribed to both presentations of Pulvinal. The data was being used out of context and the claim had not been substantiated, a breach of the Code was ruled.

AstraZeneca noted the claim 'Clearly effective' appeared as the heading to page 6 of the detail aid, the same page featured two graphs presenting the results of a comparative clinical study (Dal Negro, data on file). The first graph showed results of mean FEV1 in patients treated with Pulvinal Beclometasone Dipropionate (BDP) 800mcg daily compared with budesonide Turbohaler 800mcg daily. The second graph showed the results of rescue medication requirements in patients treated as above. However the actual study design was such that each dose of both Pulvinal BDP and budesonide was given in 200mcg doses four times a day. In the UK, budesonide (Pulmicort) was not licensed for a four times a day dosing regimen in adults. The licence did however allow a more divided regimen for budesonide but such dosing was reserved for times of severe asthma. AstraZeneca considered that not only was the clinical relevance of presenting results of a trial using non-recommended dosages lost but also the message conveyed to the prescriber was both inaccurate and misleading.

The Panel noted that the licensed dose of Pulmicort (budesonide turbohaler) was 200mcg twice daily, in the morning and in the evening. During periods of severe asthma the daily dosage could be increased up to 1600mcg. In patients well controlled the daily dose might be reduced below 400mcg, but should not go below 200mcg. The licensed dose of Pulvinal Beclometasone Dipropionate in mild asthma was 200-400mcg per day. In moderate and severe asthma the starting dose could be 800 to 1600mcg per day (ref SPC).

Dal Negro data on file compared the efficiency and tolerability of Pulvinal Beclometasone Dipropionate and Pulmicort when both were administered at a dose of 200mcg four times daily (800mcg/day). The Panel noted that when doses of more than 400mcg/day of Pulmicort were needed the SPC was not clear as to whether the total daily dose had to be given in two divided doses; AstraZeneca had submitted that the licence did allow a more divided regimen for budesonide in times of severe asthma. The Panel did not consider that the administration of Pulmicort 200mcg four times daily was inconsistent with the dosage recommendations given in the SPC. The Panel noted that the graphs stated the total daily doses of Pulvinal and Pulmicort but did not state that they had been given in four divided doses. The Panel considered that this information would have been helpful but did not consider that the graphs were misleading in that regard. No breach of the Code was ruled.

AstraZeneca noted the claim 'Clearly cost effective' appeared as the heading to page 7 of the detail aid, the page also featured a table which listed a number of inhaled asthma medications, including steroids and short acting bronchodilators, and the different devices in which they were presented. The unit strength of each presentation and the number of actuations recommended per day were also listed together with the overall cost over 365 days for each. The final column was a calculation showing the annual percentage saving with Pulvinal as compared with all other products listed. However this was on the assumption that both beclometasone and budesonide; salbutamol and terbutaline were dose equivalent irrespective of delivery device.

However although the prices and associated calculations were correct according to the cited reference MIMS they could not be used to support the claim for cost effectiveness.

AstraZeneca stated that for reasons outlined in above, this claim was not based, as it should be, on

clinical effectiveness as well as cost alone. In the absence of appropriate data such a claim was alleged to be inaccurate and misleading.

The Panel noted its comments above with regard to the meaning of the term cost effective. All of the devices shown in the table were more expensive than the Pulvinal devices. In the Panel's view the table of data compared acquisition costs only, there was no data to show that all of the devices and the doses listed exhibited equivalent efficacy. In that regard the Panel noted that for salbutamol, although the cost of Pulvinal Salbutamol 200mcg/day was listed so were four other presentations of salbutamol at a dose of 400mcg/day. The Panel considered that it was misleading and inaccurate to present such a table under the heading of 'Clearly cost effective' and breaches of the Code were ruled.

The 'Dear Colleague' letter had been sent to primary and secondary care health professionals with a special interest in the prescribing of respiratory medicines.

AstraZeneca noted that the fourth paragraph contained the sentences 'Pulvinal is the smallest multidose inhaler available in the UK and is very easy to use. This should encourage compliance – which should, in turn, help reduce the economic burden of asthma'. To make the assumption that the features of Pulvinal, which could improve compliance, could then lead to a reduction in the economic burden of asthma was an exaggeration and extrapolation of any benefit of the product. AstraZeneca alleged that making such a statement in the absence of supporting evidence rendered the mailer misleading.

The fifth paragraph of the mailer started 'Pulvinal is the only inhaler range with a transparent drug reservoir …. This means they should not have to run out of medication unexpectedly and should not need to request unnecessary prescriptions to guard against this'. AstraZeneca was unaware of any evidence which supported the theory that patients possessed more than one inhaled steroid inhaler in fear of running out unexpectedly. AstraZeneca was aware that asthma patients chose to have a number of rescue medication inhalers in various convenient places. However this was so that their rescue medication was accessible during times when instant relief was required and not from the point of view that they were unsure as to when each inhaler might run out.

Furthermore, many other asthma inhalers, although not transparent, did have a dose counter or at least a dose indicator to alert the patient when their medication needed renewing. Therefore being transparent was not a feature of the Pulvinal device that exclusively allowed the patient to gauge when a new prescription from their GP was needed. AstraZeneca alleged that to imply as such was inaccurate and misleading.

The Panel noted that the letter stated that the small size of the Pulvinal device and its ease of use 'should encourage compliance – which should, in turn, help reduce the economic burden of asthma'. Although Trinity had submitted articles by Phillips and Halloram which agreed with this statement the articles in themselves did not provide supporting evidence to show that Pulvinal would encourage compliance and reduce the economic burden of asthma. The Panel considered that the statement in the letter was thus exaggerated and misleading given the lack of data and breaches of the Code were ruled.

The fifth paragraph of the letter referred to the fact that Pulvinal was the only device with a transparent drug reservoir, allowing the patient to see how much was left thus obviating the need to request extra inhalers to ensure that they did not run out of medication unexpectedly. The Panel noted its comments regarding the potential additional benefits in terms of cost effectiveness of the transparent reservoir above. The Panel noted that no data had been submitted to show the potential additional benefits of Pulvinal actually accrued. Furthermore, there were other devices which 'warned' patients when they were about to run out of medication. The Panel considered that the letter implied that Pulvinal was the only inhaler which allowed patients to gauge when a new prescription from their GP was needed and this was not so. Breaches of the Code were ruled.

Following unsuccessful inter-company discussions AstraZeneca UK Limited complained about a journal advertisement for Pulvinal dry powder inhalers issued by Trinity Pharmaceuticals Ltd.

In addition AstraZeneca also highlighted a Pulvinal detail aid (ref TR250 July 2001) and 'Dear Colleague' letter (ref TR385 October 20001) with which it had similar concerns. Pulvinal inhalers delivered either salbutamol or beclometasone.

With regard to the cited unsuccessful inter-company discussions, Trinity noted that it had previously received one letter (loosely dated November 2001) from AstraZeneca regarding Pulvinal journal advertisements TR343 (referred to in this complaint) and TR341 (which was not mentioned in this complaint). Trinity responded promptly to AstraZeneca, offered a concession on one of its issues, and invited it to correspond further if outstanding concerns or issues remained. The majority of the issues raised in this complaint had not been the subject of prior inter-company discussion.

1 Journal advertisement TR343 August 2001

This appeared in GP, 26 October.

COMPLAINT

AstraZeneca stated that this advertisement for Pulvinal (both salbutamol and beclometasone dipropionate) featured the claims 'Clearly cost effective' and 'This dry powder inhaler is not only amongst the least expensive, but also cost effective in other ways'. The first claim, 'Clearly cost effective', was no more than a summary of the second. However the only reference given in support of the second claim was MIMS July 2001. To claim, or indeed imply, that a medicine was cost effective required some form of economic evaluation in relation

to other prescribing options and took into account relative efficacy. The only way in which a product could claim to be cost effective compared to other products was if the cost was less than that of the others and the efficacy was equal or greater.

AstraZeneca stated that although Pulvinal was amongst the cheapest dry powder inhalers, the cited pricing information provided no evidence to suggest that its clinical efficacy was equal or greater in comparison to all other alternatives. The summary of product characteristics (SPC) for Pulvinal did not address the issue of efficacy compared to alternative treatment options. The prescriber might therefore be misled by one or both of the claims into preferentially prescribing Pulvinal on a cost effectiveness basis.

AstraZeneca alleged that the claims exaggerated the significance of the data being cited to substantiate them in breach of Clause 7.2 of the Code.

Furthermore, AstraZeneca considered that the latter part of the second claim '… but also cost effective in other ways' was misleading because without clarification as to what these 'other ways' were in which Pulvinal was cost effective, the claim was very much open to interpretation. Indeed use of the plural (ways) demanded clarification of more than one way in which Pulvinal was cost effective. AstraZeneca alleged that such ambiguity rendered the claim in breach of Clause 7.2 on this point.

RESPONSE

Trinity stated that one overriding consideration throughout should be the use of the 'Clearly …' headlines in the materials as a 'play on words' relating to the unique transparent drug reservoir of the Pulvinal device.

Trinity was pleased that AstraZeneca acknowledged that the Pulvinal dry powder inhaler range was amongst the least expensive. In citing MIMS (July 2001) as Trinity's reference, the reader could not only confirm the pricing of Pulvinal in relation to other dry powder inhaler ranges, but could also find information which indicated that the recommended dose ranges at which Pulvinal was licensed for use in the various severities of asthma were similar to those of other dry powder inhaler ranges.

Additionally, the British Thoracic Society (BTS) Guidelines (Thorax 1997) advocated the use of either budesonide or beclometasone within the same dose ranges at each of the treatment steps. Pulvinal Beclometasone Dipropionate had been studied in comparison to other beclometasone devices (Catena *et al* 1993, Michelleto *et al* 1995, De Benedictis *et al* 2000) and also in comparison to Pulmicort (budesonide) Turbohaler (Dal Negro *et al* 1999 and data on file). In all studies the efficacy of Pulvinal Beclometasone Dipropionate was at least comparable to that of the product against which it was studied. Pulvinal Salbutamol was licensed one puff when required as was AstraZeneca's product Bricanyl (terbutaline) Turbohaler. One of the studies supporting the marketing authorization for Pulvinal Salbutamol (Mereu *et al* 1995) showed that there was no significant improvement in bronchodilation when comparing two puffs of Pulvinal Salbutamol to the use of just one puff.

Consequently Trinity believed that the significance of the data cited was not being exaggerated, and that this data was only further substantiated by the additional references provided. There was no breach of Clause 7.2 of the Code.

With regard to the allegation that the claim '…, but also cost effective in other ways' was misleading without clarification of the 'other ways' in which Pulvinal was cost effective, Trinity stated that an example of one such 'other way' in which Pulvinal was cost effective was given in the next sentence, which read 'Since asthma patients can see how much medication remains they don't need to stockpile inhalers'.

The intention was not to produce an exhaustive list of the ways in which Pulvinal could prove cost effective, although there were indeed a number of ways by which this might prove to be the case. These derived from the claim made in the advertisement that Pulvinal was the only inhaler range which allowed patients to see how much medication remained. This offered a number of potential benefits which would be obvious to prescribers of asthma products, including the following: Firstly patients could clearly see how much medicine remained, they did not need to stockpile inhalers (as cited in the advertisement); Secondly patients could tell when the device still contained medicine, they would not discard a unit which was still active; and Thirdly patients could tell when the device was empty, they would not inhale from an empty unit, suffering potential deterioration in the control of their asthma symptoms. On these grounds Trinity believed that the material was not ambiguous, was entirely substantiable and did not breach Clause 7.2 of the Code.

PANEL RULING

The advertisement was headed 'Clearly cost effective'. Although the advertisement featured a close up photograph of someone holding a Pulvinal Beclometasone Dipropionate device the text beneath the photograph referred to 'This dry powder inhaler range …'. Adjacent to the product logo 'Pulvinal Salbutamol Pulvinal Beclometasone Dipropionate' appeared beneath a depiction of each device. In the Panel's view, the claims made in the advertisement had thus to be applicable to both presentations of Pulvinal.

The supplementary information to Clause 7.2 of the Code 'economic evaluation of medicines' stated that care must be taken that any claim involving the economic evaluation of a medicine was borne out by the data available and did not exaggerate its significance. Part of the claim 'This dry powder inhaler range is not only amongst the least expensive …' was referenced to MIMS July 2001. No reference was given for the rest of the claim '… but also cost effective in other ways …'. In the Panel's view the term cost effective implied more than just a simple comparison of the acquisition cost of products; other factors such as relative efficacy, incidence of side effects and the full resource cost implications of using

each medicine had to be taken into account. The Panel noted that Trinity had submitted a number of clinical papers to demonstrate that Pulvinal Beclometasone Dipropionate was as effective and well tolerated as other beclometasone devices and a budesonide turbohaler, in the treatment of stable moderate asthma. No similar comparative studies for Pulvinal Salbutamol had been submitted. The advertisement applied to both presentations of Pulvinal. The Panel considered that the claim 'Clearly cost effective' was misleading and exaggerated the significance of the data as alleged. A breach of Clause 7.2 was ruled.

The Panel noted Trinity's submission that, apart from cost, one of the other ways in which Pulvinal inhalers were cost effective was that patients did not need to stockpile inhalers for fear of running out. In this regard the Panel noted that Pulvinal inhalers had a transparent reservoir so that patients could easily see how much powder was left. In addition Trinity had submitted that because of the transparency of the inhalers patients would not discard one that was still active or inhale from one which was in fact empty, suffering potential deterioration in the control of their asthma symptoms. Trinity, however, had not submitted any evidence to support these potential benefits for Pulvinal. The Panel thus considered that the claim that Pulvinal inhalers were 'cost effective in other ways' had not been substantiated and was ambiguous as alleged. A breach of Clause 7.2 was ruled.

2 Pulvinal detail aid TR250 July 2001

This was intended for primary care health professionals and was headed 'Clearly inspired'. The front cover had a close up photograph of someone holding a Pulvinal Salbutamol inhaler in their hand. The product logo with the strapline 'The case is clear,' ran along the bottom of the page and was followed by 'Pulvinal Salbutamol Pulvinal Beclometasone Dipropionate'.

2.1 'Clearly asthma therapy should be simple'

This claim appeared as the heading to page 2.

COMPLAINT

AstraZeneca noted that the page featured four bullet points describing problems that asthma patients apparently faced, for example the fourth bullet point, 'Over 40% of asthmatic patients still suffer symptoms on most days'. Directly under this list was an image of a held Pulvinal inhaler. This positioning invited the reader to assume that prescribing Pulvinal would address these underlying problems. In the absence of supporting evidence this was inaccurate and misleading.

Furthermore the image of the Pulvinal device was juxtaposed to a quotation from the BTS Guidelines 'Before altering a treatment step ensure that the patient is having the treatment and has a good inhaler technique'. This positioning implied that the Pulvinal inhaler addressed this issue without any supporting evidence.

AstraZeneca alleged that the overall impression conveyed was inaccurate and misleading in breach of Clause 7.2 of the Code.

AstraZeneca also had a more specific concern with the third bullet point 'Many patients are unable to generate optimum flow through a turbo inhaler'. The study (Johnson *et al* 1996) upon which this claim was based was not one in which the Pulvinal device was directly compared with the Turbohaler. However within the context of the layout of this page the claim itself could imply to the reader that patients using the Pulvinal device would be able to generate optimal flow rate easier than if using the Turbohaler. In the absence of conclusive data the resulting impression conveyed was inaccurate and likely to mislead.

Optimal inspiratory flow rate (IFR) for any asthma inhaler was the flow rate which a patient needed to generate in order for the maximum amount of medicine to be delivered to the lungs in one inhalation. For the Turbohaler this was 60L/min for which 30% of the nominated dose was delivered to the lungs and at an IFR of 30L/min, 15% of the dose was delivered.

In sharp contrast, the optimal IFR for Pulvinal had yet to be determined in similar studies. However there was published *in vivo* deposition data, albeit limited, which showed that the Pulvinal device delivered between 11.7% and 14.15% at flow rates of 27.8L/min and 40L/min respectively. Although this evidence was not in the form of comparative *in vivo* deposition in the same study, the balance of this clinically relevant data clearly contradicted the intended message described above.

This section misled the prescriber into choosing Pulvinal ahead of other named devices by misrepresenting data and not presenting or taking into account relevant contradictory data.

AstraZeneca alleged that the claim was unfair and misleading in breach of Clause 7.2 of the Code. Additionally it alleged that in the absence of conclusive evidence, the claim disparaged the Turbohaler device in breach of Clause 8.1.

RESPONSE

Trinity stated that some health professionals might think that prescribing for asthma was fairly straightforward, or at least that asthma symptoms were relatively well managed. Indeed a recent study would suggest that health professionals perceived asthma symptoms to be less of a burden to patients than was actually the case (Price *et al* 1999).

The page in question was designed to highlight the fact that some asthma products that were currently prescribed did have potential limitations which the health professional should be aware of. All claims made were directly supported by the references quoted. It was then pointed out that control of asthma symptoms was perhaps not ideal in that over 40% of asthmatic patients suffered symptoms on most days. To attempt to improve control of asthma symptoms by simply increasing the dose of medication prescribed might not always be the answer, and a quote from the BTS Guidelines was

included to remind the health professional to check inhaler technique and compliance with therapy before altering a treatment step.

At no stage on this page was it suggested that Pulvinal would be the most appropriate choice of therapy in helping to address these issues. No claim was made for Pulvinal on this page, and Pulvinal was not even mentioned by name. The overall intention was to make the point that there were a number of important factors to bear in mind when prescribing asthma products. A picture of the Pulvinal device was featured on this page after the bullet points as a cue for introducing the device, which was then discussed on the following page. Trinity disputed the fact that the overall impression of this page implied that Pulvinal would always address any or all of the factors listed that should be borne in mind when prescribing any asthma inhaler.

Trinity noted that AstraZeneca had suggested that the close proximity of the quote from the BTS Guidelines to the image of a Pulvinal device implied some kind of advantage of Pulvinal over any other inhaler device, yet the quote simply referred to good practice that should be followed when prescribing any inhaler device, including Pulvinal.

In summary Trinity disputed the allegation that the page contained any inaccuracies and also the fact that this page could be seen to be misleading. There was no breach of Clause 7.2 of the Code.

Trinity noted that AstraZeneca had a more specific concern with regard to the third bullet point 'Many patients are unable to generate optimum flow through a turbo inhaler'. Yet the reference was to Johnson *et al*, 1996 in which flow rate was assessed using a device designed by AstraZeneca to assess the suitability of the Turbohaler device for individual patients. Indeed AstraZeneca went on to confirm that the optimum flow rate for Turbohaler was one that a significant proportion of patients in Johnson *et al* could not achieve. Moreover, AstraZeneca pointed out that the Turbohaler device delivered twice as much medicine to the lungs at a flow rate of 60L/min (30%) as it did at a flow rate of 30L/min (15%). There was no implication that this study made any direct comparison of Pulvinal and Turbohaler.

Trinity noted that AstraZeneca then went on to discuss lung deposition with both Pulvinal and Turbohaler at different inspiratory flow rates. Whilst this information was of questionable relevance to the contested bullet point, Trinity believed that the lung deposition data it cited for Pulvinal only supported the fact that Pulvinal did not show significant variation in total lung deposition at the two different inspiratory flow rates used in the study cited. This was in sharp contrast to the data AstraZeneca chose to cite for its own product, where there was significant variation in the amount of medicine delivered at the two flow rates quoted. Trinity therefore rejected the assertion that the Pulvinal lung deposition data quoted was contradictory to any claim made. Moreover the lung deposition data cited by AstraZeneca for Turbohaler related to an inhaled steroid (budesonide), whereas the data it cited for Pulvinal related to a bronchodilator (salbutamol).

Trinity noted that the issues raised by AstraZeneca regarding the effect of flow rate on dose delivery from Pulvinal or Turbohaler were addressed later in the detail aid in a comparative *in vitro* study. No attempt was made in the disputed bullet point to compare products. The bullet point which AstraZeneca contested represented an accurate statement of fact, which was highly relevant to a discussion regarding choice/suitability of dry powder inhalers, and was neither unfair or misleading in any way, i.e. there was no breach of Clause 7.2 of the Code. Furthermore this bullet point could not be therefore be construed as a disparaging reference to Turbohaler under Clause 8.1 of the Code.

PANEL RULING

The page in question was headed 'Clearly asthma therapy should be simple'. This was followed by four bullet points illustrating why, in some cases, asthma therapy was not simple, for example, the first and second bullet points, 'At least 50% of patients can't use their MDI correctly' and 'Some DPIs provide an inconsistent dose'. Beneath these bullet points there were the two bullet points that AstraZeneca had complained about and on the right hand side of the page was a close up photograph of a Pulvinal Beclometasone Dipropionate inhaler in someone's hand. To the left of the photograph was the quotation from the British Thoracic Society Guidelines (1997), 'Before altering a treatment step ensure that a patient is having the treatment and has a good inhaler technique'.

The page made no direct claims for Pulvinal. The Panel considered, however, that the inclusion of the photograph of a Pulvinal device and the heading 'Clearly asthma therapy should be simple' implied that such a device would overcome the difficulties listed in the four bullet points thus making asthma therapy simple. No data had been submitted to show that this was so. The Panel considered that the page gave a misleading and inaccurate impression of the benefits of the Pulvinal device. A breach of Clause 7.2 was ruled.

Within the context of the page in question the Panel considered a negative statement about a competitor would imply that the opposite was true for Pulvinal. The statement 'Many patients are unable to generate optimum flow through a turbo inhaler' thus implied that many patients were able to generate optimum flow through a Pulvinal device. No data had been submitted in this regard and so the Panel considered that the claim was misleading as alleged. A breach of Clause 7.2 was ruled.

The supplementary information to Clause 8.1, 'Disparaging References' stated that much pharmaceutical advertising contained comparisons with other products and, by the nature of advertising, such comparisons were usually made to show an advantage of the advertised product over its comparatives. Provided that such critical references to another company's products were accurate, balanced, fair etc, and could be substantiated, they were acceptable under the Code. The Panel noted that AstraZeneca stated that the optimum inspiratory

flow rate required for a Turbohaler was 60L/min. Johnson *et al* showed that in a group of 15 patients, routinely using a Turbohaler, only 3 (20%) achieved a flow rate of ≥60L/min when using a teaching device consisting of a flow meter and a Turbohaler. In a group of 117 patients who were Turbohaler naïve and after they had received training only 12 (10%) achieved this flow rate. On the evidence before it, the Panel thus did not consider that it was disparaging to state that many patients were unable to generate optimum flow through a Turbohaler. No breach of Clause 8.1 was ruled.

2.2 'Clearly appeals to patients'

This claim appeared as the heading to page 4 of the detail aid followed by six bullet points.

COMPLAINT

AstraZeneca noted that the page featured a list of, what appeared to be, six beneficial features of the Pulvinal device. Given the heading to the page the overall context in which these points were set was one that implied they were all of a perceived benefit to the patient and therefore 'appealing'.

The fifth bullet point 'Significantly easier to use than a turbo inhaler' was based upon the results of a clinical study involving two groups of patients who used either the Pulvinal or the Turbohaler device to take their asthma medication (Dal Negro *et al*, data on file). Each group was assessed on how easy they found the device to use. However the study design was not cross-over so patients were only able to gauge an impression of just one device. They were unable to directly compare devices in terms of ease of use. Therefore the study was incapable of supporting this bullet point, the significance of the results being exaggerated. AstraZeneca alleged that the resulting message was misleading in breach of Clauses 7.2 and 7.4.

The final bullet point 'Consistent doses even at low flow rates' was referenced to two studies with the results of the only comparative study, Meakin *et al* (1998), presented in a graph directly underneath. This study was *in vitro* yet this was not made obvious. The Code stipulated that care must be taken when using *in vitro* data so as to not mislead as to its significance. AstraZeneca considered that the results of this *in vitro* study had been extrapolated into the clinical situation and used to support claims around patient benefit. In the absence of appropriate clinical data to indicate the direct relevance AstraZeneca therefore believed this breached Clause 7.2.

For clinical benefits, an important feature that must be considered for all devices was *in vivo* lung deposition data. The Pulvinal device delivered between 11.7% and 14.15% at flow rates of 27.8L/min and 40L/min respectively. The deposition offered by the Turbohaler had been shown to be 15% and 30% at 30L/min and 60L/min respectively and as already discussed in point 2.1 above although this evidence was not in the form of comparative *in vivo* deposition in the same study, the balance of this clinically relevant data was in sharp contrast to the claim itself. Moreover in the context of the inhalation dynamics of an individual device, there was no evidence to support a relationship between the emitted dose and the patient benefits derived from that device.

Additionally Meakin *et al* compared the emitted dose and fine particle dose (FPD) for the Pulvinal, Turbohaler and Rotohaler devices. However results for the FPD parameter were not referred to in the graph. Although AstraZeneca maintained that *in vitro* data should not be extrapolated to support claims around patient benefits, it acknowledged that the FPD was accepted as an important measure that contributed towards predicting patient benefits from a particular device. It was misleading to omit the FPD results, especially when they showed a variability factor of 1.6 with the Pulvinal device.

The other study cited, Dal Negro *et al* 1997, only involved the Pulvinal device and was not a comparative study. However the high prominence in which the results of the comparative study had been presented on the page, i.e. a large graph underneath the bullet point, implied that this second study was also a comparative study against the Turbohaler (and Rotohaler). This was clearly incorrect resulting in a misleading impression to the reader. A breach of Clause 7.2 was alleged.

In summary the two studies being used to support a dose consistency claim were incapable of doing so and consequently breached Clause 7.4 of the Code.

In addition to the concerns over the cited references the graph occupied almost half of the page. It was important to bear in mind that this high prominence was being viewed by the prescriber in the context in which the whole was set i.e. under the title 'Clearly appeals to patients'. This gave the impression that the graph was not being used to support the individual consistency claim but the title as well. This was inaccurate and gave an overall misleading impression which AstraZeneca considered breached Clause 7.2 of the Code.

RESPONSE

Trinity stated that the intention was to highlight the features of Pulvinal which might make it appealing or beneficial to patients. Indeed the fifth bullet point 'Significantly easier to use than a turbo inhaler' stemmed from a comparative study in which this overall outcome was seen (Dal Negro *et al*, data on file). This study was not a cross-over design and therefore patients could not directly compare the devices in terms of ease of use, in the same way that patients might not get an opportunity to do so outside of the sphere of clinical studies. However, patients were randomly assigned to each arm of the study and assessed their device in terms of a number of identical criteria. There were sufficient numbers of patients in each arm of the study to show a statistically significant difference in favour of Pulvinal in terms of the overall marks that each patient group gave their particular device. The results of this study could not therefore be seen to be misleading. There was no breach of Clauses 7.2 and 7.4 of the Code.

The final bullet point was indeed referenced to two studies, one of which was an *in vitro* study (Meakin *et*

al) from which results were shown on a graph lower down the page. The supplementary information to Clause 7.2 stipulated that 'Care must be taken with the use of such data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there is data to show that it is of direct relevance and significance'. Trinity noted that in its previous response to AstraZeneca's limited attempt at inter-company discussions, it did offer to more explicitly label any *in vitro* data as such, but did not receive a reply to this gesture.

Trinity considered that the *in vitro* data used was of direct relevance and significance to a discussion about the suitability of dry powder inhaler devices. Indeed assessment of dose delivery at a number of precise flow rates could only be accurately performed *in vitro*. The data confirmed that dose delivery from the Turbohaler varied significantly over a range of flow rates, and was therefore consistent with the lung deposition data that AstraZeneca had chosen to cite for the Turbohaler, and also the assertion made by Johnson *et al* that drug deposition from the Turbohaler was determined by the patient generated flow. The Meakin data also confirmed that dose delivery from the Pulvinal device over a similar range of flow rates was more consistent/less variable than was seen to be the case with the Turbohaler. Again, this finding would be supported by the Pulvinal lung deposition data cited by AstraZeneca (Pitcairn *et al* 1994).

The bullet point above the graph was not only referenced to the Meakin *in vitro* data but also supported by Dal Negro *et al*. This study showed that the peak inspiratory flow rate generated through the Pulvinal device was not related to asthma severity, and the efficacy of inhaled salbutamol delivered via the Pulvinal device did not vary in relation to asthma severity or peak inspiratory flow rate.

For the reasons discussed above, Trinity considered that both the *in vitro* and *in vivo* references cited showed results that could be beneficial to patients. Moreover the clinical data cited in the previous two paragraphs constituted the clinical data of direct relevance to the argument that AstraZeneca alleged to be absent. Therefore there was no breach of Clause 7.2.

Trinity noted that AstraZeneca reverted to its previous discussion of lung deposition data from two separate studies, one for Pulvinal and one for Turbohaler. Again AstraZeneca asserted that this data was in sharp contrast to a claim made by Trinity, yet this argument was now being provided to contest Trinity's claim that Pulvinal gave consistent doses even at low flow rates. This claim was supported by both the *in vitro* and *in vivo* references made in its support (Meakin *et al* and Dal Negro *et al*), and also by the Pulvinal lung deposition data that AstraZeneca had introduced into the discussion. Moreover, the lung deposition data for Turbohaler that AstraZeneca had cited showed that Turbohaler did not deliver a dose at a low flow rate which was consistent with that delivered at a higher flow rate.

Trinity noted that AstraZeneca then stated that in the context of the inhalation dynamics of an individual device, there was no evidence to support a relationship between the emitted dose and the patient benefits derived from that device. Yet if this were the case, there would be no need to assess the peak inspiratory flow rates of individual patients when deciding on the suitability of one device or another. AstraZeneca and various other companies distributed devices for exactly this purpose, and health professionals recommended that such assessment should be routine (Johnson *et al*). AstraZeneca went on to acknowledge in the following paragraph of its correspondence that fine particle dose (FPD) was accepted as an important measure that contributed towards predicting patient benefits from a particular device. FPD was part of the total emitted dose.

Trinity noted that in the next paragraph AstraZeneca alleged that it was misleading to omit from the detail aid the fine particle dose results from the Meakin *et al* study. There was a limit to how much information could be included in a detail aid without losing the interest of the customer and a decision was taken to show the results for total emitted dose rather than FPD, as this message might be easier for primary care health professionals to understand. However, the FPD results were consistent with those seen for total emitted dose in that once again the variability of FPD delivered by Pulvinal across a range of flow rates was significantly less than that seen with Turbohaler.

In the next paragraph AstraZeneca alleged that the *in vivo* reference used in support of the bullet point 'Consistent doses even at low flow rates' (Dal Negro *et al*) could be perceived to be a comparative study, simply because the *in vitro* study presented graphically below the bullet point was comparative. Trinity did not believe this to be the case and there was certainly no intention to mislead to this effect. Consequently there was no breach of Clause 7.2.

Trinity noted that AstraZeneca then summarised that the two studies used to support the dose consistency claim were incapable of doing so and that there was a consequent breach of Clause 7.4 of the Code. For all the reasons discussed above this was factually incorrect.

Trinity noted that AstraZeneca had expressed concern over the size of the graph of the results of the Meakin study. All graphical representation of data in this detail aid was of a size which made the graph easy to read and interpret. Moreover the graph highlighted that Pulvinal delivered a consistent dose, which should be appealing to asthmatic patients who demonstrated significant inter- and intra-subject variation in flow rate, often over short periods of time. Therefore these results, along with all other factors listed on the page, might be of appeal to patients and therefore supported the title. Consequently there was no breach of Clause 7.2 of the Code.

PANEL RULING

The claim 'Significantly easier to use than a turbo inhaler' was referenced to Dal Negro *et al*, data on file. This was an open, parallel group study in which 82 patients previously using a beclometasone MDI were randomised to receive either beclometasone from the

Pulvinal device or budesonide from a turbo inhaler. Patient opinion of ease of use was one of the secondary efficacy variables. Seventy eight percent of patients using the Pulvinal device rated it as excellent, 19% as good and 3% as moderate; 38% of patients using the turbo inhaler rated it as excellent, 49% as good and 13 % as moderate. A comparison between groups showed a statistically significant difference ($p<0.01$). Nonetheless the Panel considered that the claim implied that patients had been able to compare both devices and found the Pulvinal device 'significantly easier to use than a turbo inhaler' which was not so. The Panel considered that the claim was thus misleading and that it had not been substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

The lower half of the page featured a graph showing the effect of flow rate on mean emitted dose delivered from a Pulvinal device, a turbo inhaler and a rota inhaler. The study from which the graph had been taken, Meakin *et al*, was an *in vitro* study. The Panel noted that it was a principle under the Code that all claims etc were assumed to refer to the clinical situation unless otherwise stated.

The graph appeared on a page in which the heading referred to patients, and so, in the Panel's view, readers would expect that all of the data on the page would also refer to patients. The graph did not state that it was adapted from an *in vitro* study. Such data also had to be relevant to the clinical situation. The Panel considered that the presentation of the graph was thus misleading as alleged. A breach of Clause 7.2 was ruled. The Panel considered that this ruling covered the allegation that the graph was not being used to support the dose consistency claims but the heading as well and made no additional ruling in that regard.

The claim 'Consistent doses even at low flow rates' was referenced to Meakin *et al* and also to Dal Negro *et al* (1997). The Panel did not consider that, because data from the comparative study by Meakin *et al* had been depicted in the graph below the claim, readers would assume that Dal Negro *et al* was also a comparative study. The claim itself did not imply a comparison with other devices. No breach of Clause 7.2 was ruled on this narrow point, although the Panel noted its ruling above with regard to the use of *in vitro* data to support what otherwise appeared to be a clinical claim.

The *in vitro* study by Meakin *et al* showed that beclometasone emission from the Pulvinal device varied only slightly over the flow rate range of 28 to 63L/min which was the range of clinical interest. The fine particle dose was more sensitive to increases in flow rate, increasing by a factor of 1.6 from 22 to 35mcg. These variations were less than those observed with the Turbohaler. In their introduction the authors explained that the nature of the aerosol cloud generated from powder inhalers depended upon a complex interaction of three factors: the force of the inspiration, the design of the device, and the formulation of the powder it contained. In the Panel's view this meant that while Meakin *et al* was provided to support a claim for consistent emission of doses over a range of flow rates it applied only to Pulvinal Beclometasone Dipropionate; the results could not be assumed to apply to Pulvinal Salbutamol. The detail aid referred to both presentations of Pulvinal. The Dal Negro *et al* study did not measure the doses emitted but did show that the efficacy of salbutamol delivered via a Pulvinal device was not dependent upon generated peak inspiratory flow rate. The study measured 18 patients with moderate or severe asthma. Given the data the Panel considered that the claim was misleading and had not been substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

2.3 'Clearly benefits you'

This claim appeared as the heading to page 5 of the detail aid.

COMPLAINT

AstraZeneca noted that the page featured four bullet points, of which one was 'Reliable, consistent drug delivery'. However this claim was based on the results of the Meakin *et al* study which, as mentioned previously, was not a drug consistency study but one which measured the relationship between IFR and % emitted dose and FPD with Pulvinal. AstraZeneca believed the data was being used out of context and was by implication inaccurate. This rendered the claim unsubstantiated and likely to mislead and therefore breached Clause 7.2 on both these counts.

RESPONSE

Trinity stated that it believed that the Meakin study, for all the reasons previously discussed, demonstrated reliable, consistent drug delivery by the Pulvinal device. Trinity believed it would be extremely unlikely that any primary care reader, especially in the overall context of this detail aid, would interpret this claim in any way other than that described above. In the most unlikely event that this claim was interpreted as being a claim relating to the consistency of the formulation of the dose available for inhalation, the claim could be substantiated by providing data on the consistency of the formulation used, which was indeed reliable and consistent. As the claim could be substantiated and there was no intention to mislead, so there was no breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted its comments in point 2.2 above regarding the design of the Meakin *et al* study and its applicability to Pulvinal Salbutamol. An *in vitro* study was being used to support what would be assumed to be a clinical claim and the results from the study, which were specific to Pulvinal Beclometasone Dipropionate, were being ascribed to both presentations of Pulvinal. The data was being used out of context and the claim had not been substantiated. A breach of Clause 7.2 was ruled.

2.4 'Clearly effective'

This claim appeared as the heading to page 6 of the detail aid.

COMPLAINT

AstraZeneca noted that the page featured two graphs presenting the results of a clinical study. It was important to point out that this was the only comparative study with regard to Pulvinal Beclometasone Dipropionate and budesonide Turbohaler (Dal Negro, data on file).

The first graph showed results of mean FEV_1 in patients treated with Pulvinal Beclometasone Dipropionate (BDP) 800mcg daily compared with budesonide Turbohaler 800mcg daily. The second graph showed the results of rescue medication requirements in patients treated as above.

However the actual study design was such that each dose of both Pulvinal BDP and budesonide was given in 200mcg doses four times a day. In the UK, budesonide (Pulmicort) was not licensed for a four times a day dosing regimen in adults, instead a 200mcg twice daily or 400mcg twice daily dosage was recommended which could be reduced to 400mcg od or below in controlled patients. The licence did however allow a more divided regimen for budesonide but such dosing was reserved for times of severe asthma.

Not only was the clinical relevance of presenting results of a trial using non-recommended dosages lost but also the message conveyed to the prescriber was both inaccurate and misleading. A breach of Clauses 7.2 and 7.3 was alleged.

RESPONSE

Trinity stated that AstraZeneca rightly pointed out that the study referenced on this page was the only comparative study between Pulvinal Beclometasone Dipropionate and budesonide Turbohaler. It was therefore deemed that to provide this information would lead to more informed clinical decisions being made than would be the case in the absence of any comparative data.

Whilst the daily dose might have been given at more frequent intervals than AstraZeneca would normally recommend for Pulmicort Turbohaler in the UK, a higher frequency of dosing was not precluded by the UK Pulmicort Turbohaler marketing authorization, and was certainly no less effective than once daily or twice daily dosing of budesonide: in its response AstraZeneca confirmed that it advised more frequent dosing of Pulmicort Turbohaler in times of severe asthma. Therefore the data related to a dosage regimen which was not precluded by the Pulmicort Turbohaler marketing authorization and could not therefore be misleading. Nor was the data inaccurate. Therefore there was no breach of Clauses 7.2 or 7.3 of the Code.

PANEL RULING

The licensed dose of Pulmicort (budesonide turbohaler) was 200mcg twice daily, in the morning and in the evening. During periods of severe asthma the daily dosage could be increased up to 1600mcg. In patients well controlled the daily dose might be reduced below 400mcg, but should not go below 200mcg (ref Pulmicort SPC, Electronic Medicines Compendium). The licensed dose of Pulvinal Beclometasone Dipropionate in mild asthma was 200-400mcg per day. In moderate and severe asthma the starting dose could be 800 to 1600mcg per day (ref SPC).

The Dal Negro study data on file, had compared the efficiency and tolerability of Pulvinal Beclometasone Dipropionate and Pulmicort when both were administered at a dose of 200mcg four times daily (800mcg/day). The Panel noted that when doses of more than 400mcg/day of Pulmicort were needed the SPC was not clear as to whether the total daily dose had to be given in two divided doses; AstraZeneca had submitted that the licence did allow a more divided regimen for budesonide in times of severe asthma. The Panel did not consider that the administration of Pulmicort 200mcg four times daily was inconsistent with the dosage recommendations given in the SPC. The Panel noted that the graphs stated the total daily doses of Pulvinal and Pulmicort but did not state that they had been given in four divided doses. The Panel considered that this information would have been helpful but did not consider that the graphs were misleading in that regard. No breach of Clauses 7.2 and 7.3 was ruled.

2.5 'Clearly cost effective'

This claim appeared as the heading to page 7 of the detail aid.

COMPLAINT

AstraZeneca noted that the page featured a table which listed a number of inhaled asthma medications, including steroids and short acting bronchodilators, and the different devices in which they were presented. The unit strength of each presentation and the number of actuations recommended per day were also listed together with the overall cost over 365 days for each.

The final column was a calculation showing the annual percentage saving with Pulvinal as compared with all other products listed. However this was on the assumption that both beclometasone and budesonide; salbutamol and terbutaline were dose equivalent irrespective of delivery device.

However although the prices and associated calculations were correct according to the cited reference MIMS they could not be used to support the claim for cost effectiveness.

AstraZeneca stated that for reasons outlined in point 1 above, this claim was not based, as it should be, on clinical effectiveness as well as cost alone. So in the absence of appropriate data such a claim was alleged to be inaccurate and misleading in breach of Clauses 7.2 and 7.4.

RESPONSE

Trinity referred to point 1 above and submitted there were no breaches of either Clause 7.2 or Clause 7.4 of the Code.

PANEL RULING

The Panel noted its comments in point 1 above with regard to the meaning of the term cost effective. The page at issue featured a table of data comparing the costs of various beclometasone devices and various salbutamol devices. All of the devices shown were more expensive than the Pulvinal devices. Although in its response to point 1 Trinity had submitted clinical data which demonstrated that Pulvinal Beclometasone Dipropionate was as effective and well tolerated as other beclometasome devices and a budesonide inhaler, in the treatment of stable moderate asthma no comparable data for Pulvinal Salbutamol had been submitted. In the Panel's view the table of data compared acquisition costs only, there was no data to show that all of the devices and the doses listed exhibited equivalent efficacy. In that regard the Panel noted that for salbutamol, although the cost of Pulvinal Salbutamol 200mcg/day was listed so were four other presentations of salbutamol at a dose of 400mcg/day. The Panel considered that it was misleading and inaccurate to present such a table under the heading of 'Clearly cost effective'. Breaches of Clause 7.2 and 7.4 were ruled.

3 'Dear Colleague' letter TR 385 October 2001

This had been sent to primary and secondary care health professionals with a special interest in the prescribing of respiratory medicines.

COMPLAINT

AstraZeneca noted that the fourth paragraph contained the sentences 'Pulvinal is the smallest multidose inhaler available in the UK and is very easy to use. This should encourage compliance – which should, in turn, help reduce the economic burden of asthma'.

To make the assumption that the mentioned features of the Pulvinal device, which could improve compliance, could then lead to a reduction in the economic burden of asthma was a gross exaggeration and extrapolation of any benefit of Pulvinal. AstraZeneca alleged that making such a statement in the absence of supporting evidence rendered the mailer misleading in breach of Clauses 7.2 and 7.10.

The fifth paragraph of the mailer started 'Pulvinal is the only inhaler range with a transparent drug reservoir …. This means they should not have to run out of medication unexpectedly and should not need to request unnecessary prescriptions to guard against this'.

AstraZeneca was unaware of any evidence which supported the theory that patients possessed more than one inhaled steroid inhaler in fear of running out unexpectedly. AstraZeneca was aware that asthma patients chose to have a number of rescue medication inhalers in various convenient places. However this was so that their rescue medication was accessible during times when instant relief was required and not from the point of view that they were unsure as to when each inhaler might run out.

Furthermore, many other asthma inhalers, although not transparent, did have a dose counter or at least a dose indicator to alert the patient when their medication needed renewing. Therefore being transparent was not a feature of the Pulvinal device that exclusively allowed the patient to gauge when a new prescription from their GP was needed. AstraZeneca alleged that to imply as such was inaccurate and misleading in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Trinity stated that it was pleased that AstraZeneca acknowledged that the features described could improve compliance. There were many references available to suggest that improvement in compliance with any asthma therapy could help to reduce the economic burden of asthma. Specifically, each copy of this mailing included a copy of Evidence Based Medicine in Practice (September 2001), which it invited the customer to read. The conclusion to the article by Ceri Phillips stated that 'The Pulvinal device has been designed to facilitate ease of use. This, together with its portability, should result in good adherence rates'. The author went on to state that 'There are grounds for suggesting that, in terms of the cost-effectiveness plane, the Pulvinal device range would be located in the dominant quadrant, or, at worst, on the horizontal axis between the dominant and cost-effective quadrants'. The article by Dr Halloran stated that 'The cost of not adequately treating asthma easily outweighs the cost of using devices such as Pulvinal in every case. I would agree that the ease of use of these devices and the ability to see how much drug is remaining at all times are attractive features and may enhance patient compliance'. Therefore supporting evidence was not absent and no breach of Clauses 7.2 or 7.10 had occurred.

'Pulvinal is the only inhaler range with a transparent drug reservoir …. This means they should not have to run out of medication unexpectedly and should not need to request unnecessary prescriptions to guard against this'.

Firstly Trinity disputed AstraZeneca's selective and factually incorrect quoting of the copy. The contested copy actually read 'Pulvinal is the only inhaler range with a transparent drug reservoir. This allows asthma patients to see how much powder they have left at any time. This means they should not run out of medication unexpectedly and should not need to request unnecessary prescriptions to guard against this'.

Trinity was pleased that AstraZeneca acknowledged that patients might have more than one inhaler in more than one place, even if this was only believed to be the case with the blue inhaler. When a patient had more than one inhaler in more than one place over a period of time, it was unlikely that they would remember exactly how many doses had expired and how many doses remained.

Some devices did have some form of dose counter, though others had none. Indeed the dose indicator on a UK Bricanyl Turbohaler did not count down numerically, but turned red when the devices had been actuated 80 times, which did not necessarily

mean that 80 doses had been taken by the patient. For the patient who might have more than one inhaler in more than one place, it might prove difficult to remember how many of the remaining 20 actuations had been made since the indictor turned red. To discard the unit with 20 actuations remaining would not be cost effective. To continue to inhale from the device more than 20 times after the indicator had turned red could mean that the patient was inhaling from an empty device which they were depending on to provide rescue medication. This could lead to the deterioration of asthma symptoms. The situation was even more complicated with devices that had no counter and/or means of visual inspection of the medication. Consequently leading authors (e.g. Levy *et al*) of patient publications advocated that a spare inhaler should always be kept and did not confine this advice to bronchodilators. Trinity did not claim that indication of the number of doses remaining in some other devices was not possible to some extent and so the allegations of being inaccurate and misleading were misplaced. Therefore there was no breach of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The letter stated that the small size of the Pulvinal device and its ease of use 'should encourage compliance – which should, in turn, help reduce the economic burden of asthma'. Although Trinity had submitted articles by Phillips and Halloram which agreed with this statement the articles in themselves did not provide supporting evidence to show that Pulvinal would encourage compliance and reduce the economic burden of asthma. Phillips noted that patient compliance might be a possible benefit but noted that there was no conclusive evidence for this at present. The Panel considered that the statement in the letter was thus exaggerated and misleading given the lack of data. Breaches of Clauses 7.2 and 7.10 were ruled.

The fifth paragraph of the letter referred to the fact that Pulvinal was the only device with a transparent drug reservoir thus allowing the patient to see how much was left thus obviating the need to request extra inhalers to ensure that they did not run out of medication unexpectedly. The Panel noted its comments regarding the potential additional benefits in terms of cost effectiveness of the transparent reservoir in point 1 above. The Panel noted that no data had been submitted to show the potential additional benefits of Pulvinal actually accrued. Furthermore, there were other devices which 'warned' patients when they were about to run out of medication; for example with the clickhaler patients were able to tell when there were only ten doses left and there was a lockout mechanism after the final dose. The Panel considered that the letter implied that Pulvinal was the only inhaler which allowed patients to gauge when a new prescription from their GP was needed and this was not so. Breaches of Clauses 7.3 and 7.2 were ruled.

During the consideration of this point the Panel noted that the 'Dear Colleague' letter had been sent out with the September 2001 issue of the review 'Evidence Based Medicine in Practice' entitled 'A cost effectiveness analysis of asthma delivery devices'. This review contained many references to the Pulvinal device and prescribing information for both presentations of Pulvinal was included on the back cover. The review was 12 pages long. There was, however, no clear reference to where the prescribing information could be found as required in the case of printed promotional material consisting of more than four pages and as stated in Clause 4.8 of the Code. The Panel requested that Trinity be advised of its concerns in this regard.

Complaint received **26 March 2002**

Case completed **20 June 2002**

HEALTH AUTHORITY ASSISTANT DIRECTOR, MEDICINES AND PRESCRIBING v PHARMACIA AND PFIZER

Celebrex leaflet

A health authority assistant director, medicines and prescribing, complained that a Celebrex (celecoxib) leavepiece, issued by Pharmacia and Pfizer, misquoted guidance from the National Institute of Clinical Excellence (NICE) regarding the use of COX-2 selective inhibitors. The leavepiece listed a number of patient groups, including those with a history of gastrointestinal ulcers, bleeds or perforations or serious co-morbidity, in whom COX-2 selective inhibitors should be used in preference to standard NSAIDs. The complainant stated that the NICE guidance actually said that in patients with a history of gastrointestinal ulcers, bleeds or perforations or serious co-morbidity very careful consideration of any agent, even a selective COX-2 agent, was required.

The Panel rejected the companies' submission that prescribers might refer to the NICE guidance for further detail; the leavepiece had to be a stand alone item and not rely on reference to the NICE guidance for clarification. The submission that the leavepiece served as a useful reminder of the guidance on COX-2 inhibitors was also rejected. The NICE guidance stated 'The risk of NSAID-induced complications is particularly increased in patients with a previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation. The use of even a Cox II selective agent should therefore be considered especially carefully in this situation'.

The Panel noted the submission that by emphasising the words *'in preference to standard NSAIDs'* in the leavepiece the companies had presupposed that the clinician had made the appropriate risk/benefit assessment. The patient groups listed needed different risk/benefit assessments. Although the leavepiece correctly described one group of potentially high risk patients as those with 'Previous clinical history of upper GI ulcers, bleeds or perforations', it did not state, as did the NICE guidance, that this group was particularly vulnerable to GI complications and that the use of even COX-2 agents should be considered especially carefully in this situation. The Panel considered that the leaflet was misleading in this regard; a breach of the Code was ruled.

The Panel noted that the complainant stated that the patient group with serious co-morbidity needed similar especially careful consideration before considering prescribing a COX-2 selective agent according to the NICE guidance; this was not so. No breach of the Code was ruled in this regard.

A health authority assistant director, medicines and prescribing, complained about a leavepiece (ref A43303) for Celebrex (celecoxib) which referred to guidance from the National Institute for Clinical Excellence (NICE). The leavepiece bore the names of Pharmacia Limited and Pfizer Limited and the matter was taken up with both companies.

The leavepiece stated that the NICE guidance was that Cox-2 selective inhibitors should be used in preference to standard NSAIDs in the following groups of patients with OA [osteoarthritis] and RA [rheumatoid arthritis]:

- patients aged 65 or over*

or in any of the other following patient groups:

- prolonged use of standard NSAIDs at the maximum recommended doses
- previous clinical history of upper GI ulcers, bleeds or perforations
- co-prescribed with medications known to increase the likelihood of upper GI adverse events
- serious co-morbidity.

The asterisked footnote stated '58% of OA patients in the UK are over the age of 65'. The product logo appeared at the bottom of the leavepiece with the strapline '200mg once daily in OA'.

COMPLAINT

The complainant stated that the leavepiece appeared to misquote NICE guidance and noted that the guidance actually said that very careful consideration of any agent, even a Cox-2 selective agent, was required in patients with serious co-morbidity or previous GI bleeds or perforations.

When writing to Pharmacia and Pfizer the Authority asked them to bear in mind the requirements of Clause 7.2 of the Code.

RESPONSE

Pharmacia and Pfizer submitted separate but identical responses.

By way of background, the companies stated that the leavepiece was for health professionals which provided, on the front, a summary of the NICE guidance on the use of cyclo-oxygenase (Cox 2) selective inhibitors. The companies stressed that the item did not give the impression that the material was quoted directly from the guidance.

The remit of NICE was to appraise new technologies in terms of their clinical and cost effectiveness. It was intended that its recommendations would be implemented throughout the NHS to avoid the inequity in healthcare that had been the subject of considerable publicity in recent years.

The companies supported the aims of NICE and wished to see patients in England and Wales having equal access to advances in the management of osteo- and rheumatoid arthritis. Reproducing the entire guidance document, or a comprehensive summary of it, was not possible on such an item. The companies had therefore publicised the main recommendations

of the guidance in order to raise awareness of it among a wide body of prescribing health professionals. The audience that this item was aimed at was a sophisticated and sceptical one which would recognise that this was a summary of the main recommendations rather than a comprehensive summary of the whole guidance. Indeed, reference to the guidance was clearly included on the item in order that prescribers might refer to it for further detail. As a result the item could not be seen as misleading. The companies believed this to be a responsible approach and had received no criticism from NICE itself. In addition, there was no suggestion in the complaint that the item presented a danger to patients by the way in which it was set out. These factors supported the companies' view that the piece was responsible both in its aims and in its execution.

The leavepiece, in the form of a double sided card, served as a useful reminder of the guidance for prescribers on where a COX-2 selective inhibitor should be used in preference to *standard NSAIDs* when used in conjunction with the full appraisal document which was some 18 pages in length.

NICE had clearly recognised that the COX-2 selective inhibitors demonstrated equivalent efficacy to the traditional NSAIDs but with a superior gastrointestinal tolerability (see for example sections 4.2 and 4.3 of the NICE guidance). Following a review of the economic impact, NICE recommended that COX-2 selective inhibitors should be used in preference to standard NSAIDs only in 'high risk' patients.

The item in question stated that 'COX-2 selective inhibitors should be used *in preference to standard NSAIDs* in the following group of patients with OA and RA'. There was no suggestion that these agents should be used in all patients with serious co-morbidity or previous upper GI bleeds or perforations. By emphasising with italics the words '*in preference to standard NSAIDs,* the companies had pointedly presupposed that the clinician had made an appropriate risk/benefit assessment and, in the absence of a COX-2 selective inhibitor, would have decided to prescribe a standard NSAID. In the 'high risk' patients defined by NICE and listed in this item, NICE had clearly stated that COX-2 selective inhibitors offered advantages to patients (section 4.3 of the NICE guidance) and should be used, in preference to standard NSAIDs, when clearly indicated as part of the management of RA or OA (section 1.3 of the guidance). The companies were unaware of any co-morbid conditions in which the COX-2 selective inhibitors were contraindicated that were not also contraindications for standard NSAIDs.

The companies agreed that where patients had a history of gastroduodenal ulceration or serious co-morbidity the use of even a COX-2 selective inhibitor should be considered especially carefully. The companies did not, however, consider this item in breach of Clause 7.2 of the Code as no reference was made in it to where different treatment modalities should be employed in varying clinical situations. As commented on above, this item simply informed prescribers where a COX-2 selective inhibitor should be used *in preference to standard NSAIDs,* once the decision had been made to prescribe a standard NSAID in place of another therapeutic option.

The companies shared the ABPI's aim to ensure that clinicians were appropriately informed about therapies in a balanced and accurate way but did not consider that the exposure afforded to the guidance by items such as this would encourage misuse. The companies did not believe that the item in question, when read in its proper context, could mislead prescribers into making unsafe prescribing decisions. They considered that the item was not inconsistent with the guidance, was not misleading and did not encourage irrational use of the product, particularly in groups outside those which were identified by NICE.

PANEL RULING

The Panel accepted that the leavepiece did not give the impression that it quoted directly from the NICE guidance. Although reference to the NICE guidance was included on the leavepiece the Panel did not accept the submission that this meant that prescribers might refer to it for further detail and that as a result the leavepiece could not be seen as misleading. The leavepiece had to be a stand alone item and not rely on prescribers reading the NICE guidance for clarification. In this regard the Panel also rejected the companies' submission that the leavepiece served as a useful reminder of the guidance on where to use COX-2 inhibitors when used in conjunction with the full appraisal document.

The NICE guidance referred to in the leavepiece was entitled 'Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis'. Section 1.3 of the guidance stated 'Cox II selective inhibitors are not recommended for routine use in patients with rheumatoid arthritis (RA) or osteoarthritis (OA). They should be used, in preference to standard NSAIDs, when clearly indicated as part of the management of RA or OA only in patients who may be at 'high risk' of developing serious gastrointestinal adverse effects'.

Section 1.4 of the NICE guidance described high risk patients. The first half of the paragraph identified such patients as those aged 65 years or over, those taking concomitant medicines known to increase the likelihood of upper GI adverse events, those with a serious co-morbidity or those requiring prolonged use of maximum recommended doses of standard NSAIDs. The second half of the paragraph read 'The risk of NSAID-induced complications is particularly increased in patients with a previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation. The use of even a Cox II selective agent should therefore be considered especially carefully in this situation'.

Beneath the introductory statement in the leavepiece, 'COX-2 selective inhibitors should be used *in preference to standard NSAIDs* in the following group of patients with OA and RA', was boxed text stating 'Patients aged 65 years or over'. The leavepiece continued by stating '*or* in any of the following

patient groups': 'Prolonged use of standard NSAIDs at their maximum recommended doses', 'Previous clinical history of upper GI ulcers, bleeds or perforations', 'Co-prescribed with medications known to increase the likelihood of upper GI adverse events' and 'Serious co-morbidity'.

The Panel noted the submission that by emphasising the words *'in preference to standard NSAIDs'* the companies had presupposed that the clinician had made the appropriate risk/benefit assessment. The patient groups noted needed different risk/benefit assessments. Although the second bullet point in the box of text correctly described one group of potentially high risk patients as those with 'Previous clinical history of upper GI ulcers, bleeds or perforations', it did not state, as did the NICE guidance (Section 1.4), that this group was particularly vulnerable to GI complications and that the use of even COX-2 agents should be considered especially carefully in this situation. It appeared from the leaflet that NICE considered patients in this particularly high risk group to be no more vulnerable than other high risk patients such as those aged 65 years or above which was not so. The Panel considered that the leaflet was misleading in this regard; a breach of Clause 7.2 was ruled.

The Panel noted that the complainant stated that the patient group with serious co-morbidity needed similar especially careful consideration before considering prescribing a COX-2 selective agent according to the NICE guidance; this was not so. No breach of Clause 7.2 of the Code was ruled in this regard.

During its consideration of this case the Panel noted that in the introductory statement, telling readers in which groups of patients NICE had recommended the use of COX-2 inhibitors, no mention was made of 'only in those patients who might be at a 'high risk' of developing serious GI side-effects'. The Panel considered that the omission of this information, and particularly of the word 'only' after '… standard NSAIDs', meant that readers would be unaware that, although COX-2 inhibitors were licensed for use in all adult patients with osteoarthritis or rheumatoid arthritis, the view of NICE was that they should only be used in those patients who might be at a high risk of developing serious GI side-effects. NICE was thus recommending that the use of the medicines should be more restricted than their licences allowed. The Panel was concerned that the NICE guidance had not been accurately represented in this regard and requested that Pharmacia and Pfizer be advised of its concerns.

Complaint received **3 April 2002**

Case completed **23 May 2002**

GENERAL PRACTITIONER v CROOKES HEALTHCARE

Provision of camera

A general practitioner complained about the provision of a digital camera by Crookes Healthcare.

The complainant stated that a representative of Crookes Healthcare told him that he was able to provide a digital camera for the surgery. The representative had explained that the complainant was expected to undertake a project, taking digital photographs of patients before and after the use of Crookes Healthcare's psoriasis treatment, Curatoderm (tacalcitol), which the complainant would be expected to prescribe. He offered the complainant a loan agreement, which could be terminated at any time, but set no final date. The representative intimated that Crookes Healthcare would not end the loan period as long as the complainant undertook the work involved.

The complainant completed the work and returned all the necessary material to Crookes Healthcare and was therefore surprised to receive a letter from it indicating that he had not undertaken the work and that he should return the camera. The complainant complained to Crookes Healthcare which replied that as the work had been undertaken the loan period could be extended.

The complainant alleged that this whole project was an attempt to bribe him to prescribe Curatoderm by offering him the use of a digital camera for an indefinite period in breach of the Code.

On balance the Panel did not consider that the briefing material was such that it instructed representatives that the loan of the camera was conditional on the prescribing of Curatoderm. The digital camera in question was not a gift. It was provided on loan but not on long term loan. Crookes Healthcare had asked for the cameras to be returned and this had been referred to in the loan agreement. The Panel decided that, on balance, the arrangements for the loan of the camera were not unacceptable. As the representative had left the company, it was impossible to know what had been said to the complainant. There was no evidence that the representative had used the offer of the loan of the camera as an inducement to gain an interview. The Panel ruled no breach of the Code.

A general practitioner complained about the provision of a digital camera by Crookes Healthcare Ltd in relation to the promotion of Curatoderm (tacalcitol).

COMPLAINT

The complainant stated that in November 2000 he was approached by a representative of Crookes Healthcare who initially simply told the complainant that he was able to make available a digital camera for use within the surgery. He was not specific about what this involved or what was expected of the complainant. The representative was given an appointment and he came to see the complainant at the surgery with the digital camera. When he arrived he explained that the complainant was expected to undertake a project which involved taking several digital photographs of patients before and after the use of Crookes Healthcare's psoriasis treatment, Curatoderm, which the complainant would be expected to prescribe and go on prescribing for these patients. He offered the complainant a loan agreement which indicated that the loan arrangement could be terminated at any time but set no final date for termination. The representative intimated that Crookes Healthcare would not end the loan period as long as the complainant undertook the work involved.

From the outset the complainant was apprehensive about whether this was ethical or not. However, he had a long-standing interest in dermatology and in particular in the treatment of psoriasis and at this stage would have felt somewhat uncomfortable and embarrassed about withdrawing from the agreement on the grounds that it was unethical. The complainant therefore agreed to proceed in spite of the fact that no payment was mentioned or offered for what was a quite substantial amount of work which would clearly be of benefit to Crookes Healthcare, although the benefit would appear to be one of generating material for advertising purposes rather than for any genuine clinical or scientific research.

The complainant completed the work within a period of about six months and returned all the necessary material to Crookes Healthcare.

The complainant was therefore somewhat surprised to receive a letter from Crookes Healthcare in December 2001 indicating that he had not undertaken the work asked of him and that he should return the camera. From the letter, there was absolutely no doubt whatsoever that the submission of work was linked to the loan of the camera and it was implicit within the letters of 17 December and 17 January that Crookes Healthcare would not be asking for the return of the camera had the complainant done the work it required of him, which for some reason Crookes Healthcare refused to accept the complainant had done. The letter of 17 January in particular stated that Crookes Healthcare wished to either collect the camera or that the complainant should return the images. The complainant subsequently complained about this to Crookes Healthcare who replied on 7 February and stated that in view of the fact that the complainant had undertaken the work that was asked for he could extend the loan period. The complainant alleged that it was fairly clear from the correspondence with Crookes Healthcare that this whole project was an attempt to bribe him to prescribe Curatoderm by offering him the use of a digital camera for an indefinite period. He believed that this seriously contravened the Code.

Furthermore, it was also clear that as soon as Crookes Healthcare had obtained the work it wanted it was quite happy to terminate the agreement thus obtaining a considerable amount of useful work

without any cost to itself. The fact that this amounted to a confidence trick, played against the complainant by Crookes Healthcare, might not amount to a breach of the Code. However it was clearly a sad reflection on Crookes Healthcare.

When writing to Crookes Healthcare, the Authority asked it to bear in mind the requirements of Clauses 2, 9.1, 15.2, 15.3 and 18.1 of the Code.

RESPONSE

Crookes Healthcare rejected absolutely the suggestion that the project was a 'confidence trick'.

Background

The Crookes Digital Dermatology Programme was set up in 2000. From the initial stages, the project was reviewed by the appropriate staff in medical and regulatory affairs, legal and marketing, following the company's standard review procedure for promotional material under the Code (1998 edition). In the opinion of the reviewers, the project and the associated printed materials were not promotional in design or intent, and therefore did not fall within the strict remit of the Code. However, the project was approved as complying with the relevant sections of the Code.

The company had identified a need to obtain a collection of good photographs of skin conditions seen in general practice, with a particular emphasis on, but not restricted to, psoriasis. The original concept envisaged that, over a period time, the scheme would focus on a number of different skin conditions in turn. It was expected that these pictures would be used in a range of promotional publications related to Crookes Healthcare's skincare range of products. A number of digital cameras, capable of taking clinical pictures of adequate quality, were supplied to suitable doctors on loan, and this was clearly stipulated in the initial letters and in a signed loan agreement.

The initial selection of potential participants was made by Crookes Healthcare's representatives (territory managers) who were asked to identify GPs in their territory who had an interest in dermatology, and who saw sufficient cases to be able to make a worthwhile contribution to the picture library. Names were submitted to Crookes Healthcare's marketing department and once the name had been approved by a senior member of the marketing team, the territory managers each approached the doctors on their territory inviting them to take part. In all 24 were eventually selected to enter the project. The brief given to them asked for pictures of skin conditions, preferably both before and after treatment. Crookes Healthcare's interest in psoriasis was made clear and as manufacturers of Curatoderm it anticipated that this would be one of the treatments chosen. Treatment choice was to be made solely on the basis of the doctor's 'clinical judgement and discretion' (as stated in the loan agreement) and there was no obligation to use Curatoderm. Use of Crookes Healthcare's product was not a pre-condition of taking part in the photographic programme. The clinician's briefing document, supplied to the doctor, stated 'It should be stated that the prescription of any Crookes' product is entirely at the discretion of the clinician, and the loan of a camera to record dermatological conditions is in no way provided in exchange for the prescription of Crookes' products.' The participating doctors undertook to obtain full written consent of the patient before taking any pictures.

Once doctors agreed to take part in the study, the scheme was administered by ScopeMedical, a publishing company which was working with Crookes Healthcare to produce a range of educational and promotional materials.

The camera chosen for the project was the Fuji-film MX 1500, which was capable of reproducing skin tones accurately and which had the facility of focussing very close to the subject, while being simple to operate. This specification ensured that the pictures obtained would be suitable for the intended purpose. In all 30 cameras were purchased by Crookes Healthcare at a cost of approximately £170 each (+VAT).

In the loan agreement, Crookes Healthcare recognised that the camera could (and probably would) be used to record other clinical material, not directly related to Crookes Healthcare, the psoriasis programme or Crookes Healthcare's products. This was acceptable, although Crookes Healthcare stipulated that any such use should not use the recording medium (SmartMedia cards) supplied by Crookes Healthcare, but alternative SmartMedia cards should be purchased from high-street electrical retailers.

The loan agreement

A copy of the agreement, signed by the complainant on 16 November 2000, was provided. The key points made in the agreement were:

- The camera was loaned for a period (not stated), and the loan could be terminated by either party with one month's written notice.
- The purpose of the project was 'to establish a library of patient photographs for use by healthcare professionals for educational purposes … Library pictures may appear in articles in professional medical journals or textbooks or be used by Crookes Healthcare in promotional materials to go to Healthcare Professionals'.
- All intellectual property rights in the photographs were to be assigned to Crookes.
- 'No payment shall be due in respect of the loan of the camera or the photographs taken on behalf of Crookes'.
- No period of loan was specified; it was intended that the project would run until a sufficient number of adequate pictures had been received. The phrase 'period of loan' appeared in the agreement, and made it clear that there was no intention that the period should be indefinite.

Closure of the project

The project ran for approximately one year. In this time the 24 doctors produced only 33 pictures and it was therefore agreed between ScopeMedical and Crookes Healthcare that the project had not been a success and should be wound up. ScopeMedical

therefore contacted all the participants, using a standard letter, stating that as no pictures had been received, the project was to be wound up, and requesting the return of the equipment. The majority of the doctors complied and the cameras had been returned. Unfortunately, due to a clerical error at ScopeMedical, the complainant was sent the standard letter which said that he had not submitted any pictures, when in fact he had supplied ScopeMedical with 27 photographs, and thus made the greatest contribution to the scheme (one other doctor had submitted 5 pictures). He did not reply to letters sent on 17 December 2001, followed up on 17 January 2002 and 25 January, requesting the return of the equipment. When he did reply, protesting that he had submitted pictures, a letter of apology was sent from ScopeMedical, but it was made clear by ScopeMedical that Crookes Healthcare had decided to terminate the whole project ('However although you have sent these images, Crookes Healthcare Ltd have asked if we could contact all the participants in this program to return any more images and also the digital cameras, hence the reason for sending the return prepaid bag to yourself.').

The complainant then complained to the managing director of Crookes Healthcare who apologised for the misunderstandings that had occurred. It was pointed out that, under Clause 18.1, Crookes Healthcare was not able to give the camera on a permanent basis, which was why it had been the subject of a loan agreement. It was suggested that the complainant might wish to extend the loan period but no response to this was forthcoming. ScopeMedical subsequently sent a further request for the camera, which was returned to ScopeMedical on 2 April 2002.

Detailed response to the complaint
Crookes Healthcare wholeheartedly and unreservedly apologised to the complainant for the distress caused when he was inadvertently sent the standard letter, which incorrectly stated that he had not submitted any pictures, when in fact he had made the largest single contribution to the scheme.

However, Crookes Healthcare denied absolutely his claims that: the scheme expected him to prescribe and go on prescribing Curatoderm; that this was a bribe to prescribe Curatoderm; and that the scheme was a confidence trick.

In his letter of complaint, the complainant mentioned that the benefit of the scheme 'would appear to be one of generating material for advertising purposes rather than for any genuine clinical or scientific research'. Crookes Healthcare would point out that this was never claimed to be 'scientific research'; the objectives were clearly defined as 'to establish a library of patient photographs … for educational purposes'. They could also 'be used by Crookes Healthcare in promotional materials to go to Healthcare Professionals'.

The complaint in relation to provisions of the Code
Crookes Healthcare noted the request to bear in mind the requirements of Clauses 2, 9.1, 15.2, 15.3 and 18.1 of the Code and responded specifically to each of these points.

Clause 9.1 The scheme was limited to a small number of doctors who were selected for their professional standing. The briefing document which set out how a territory manager should identify a suitable doctor stated '… the selected clinician must have a recognised interest in Dermatology and see a fair number of dermatology patients in their primary care practice'. The intention, clearly stated in the briefing documents, was to obtain clinical photographic material which could be used in educational and promotional publications. In setting up the scheme, Crookes Healthcare took special care to take full account of the Code and to maintain the required high standards.

Clause 15.2 The territory manager involved in this case was one of Crookes Healthcare's senior and more experienced territory managers. Unfortunately, as a result of company restructuring, he (together with the entire field force) was made redundant and left the company some time ago. It was therefore not possible to obtain his side of the story. However, it was quite clear from the briefing documents, issued to the territory managers at the time, that they, and the clinicians, were correctly and fully briefed on the purpose and the requirements of the scheme. A flow-diagram set out the process, and specified what had to be done at each stage. Crookes Healthcare believed that the process was fully in compliance with the Code.

Clause 15.3 This scheme was not an inducement or subterfuge to gain an interview. It was a fair attempt to obtain useful photographic material. Crookes Healthcare recognised that this would involve some work, as it was necessary to record basic clinical information about each picture; it was clearly stated from the outset that no payment would be made for the pictures or for the intellectual property rights. In fact, the only 'reward' would be the professional pride from seeing one's own pictures used in print. Although doctors were free to use the camera for other clinical purposes within their practices, all materials used were to be provided at their own expense, and there was therefore no significant benefit in kind. It was also very clear from the outset that the camera was on loan and that it was not in any way to be seen as a gift. The invitation to become one of the select group of doctors in the scheme was not linked to the grant of an interview. Crookes Healthcare believed that the scheme was fully in compliance with Clause 15.3.

Clause 18.1 The camera was supplied on loan, with a formal loan agreement, solely for the purposes of obtaining clinical photographs. The camera supplied was a good quality machine, selected for its suitability for the job, and at the time the scheme was set up, it was considered a good, medium range specification. It was not branded in any way, and therefore was not a promotional item. The scheme was not intended or used as a means of gaining a interview. The initial discussion between the territory manager and the doctor was to explain the scheme, using the briefing documents which had been carefully prepared to fully comply with the Code. The complainant's letter described this process using very emotive words ('I was expected to undertake a project …', 'I would be expected to prescribe …', 'He offered me a loan agreement …'), whereas Crookes Healthcare's briefing

documents made it clear that this was 'an invitation' to participate, the prescription of Crookes Healthcare's products was 'entirely at the discretion of the clinician' and, far from it being an option, it was essential that the loan agreement was signed before the camera was handed over.

Crookes Healthcare believed that the loan was consistent with the terms of the first paragraph of the supplementary information to Clause 18.1 of the Code, in that the camera equipment could be used for recording a range of clinical material in the doctor's practice, thus enhancing patient care. It was intended that the photographs should be used for educational purposes, and this could also be seen as an enhancement to patient care, in a wider context.

Crookes Healthcare noted that under the supplementary information to Clause 18.2, 'Items provided on long term or permanent loan are regarded as gifts …'. Crookes Healthcare did not believe that this applied in this case. There was no intention of leaving the camera with the participating doctors permanently. Although the loan agreement did not specify a definite period of loan, this was because Crookes Healthcare hoped to be able to utilise the same doctors at regular intervals for collecting further series of clinical pictures, on a range of different topics. The poor response to this project led Crookes Healthcare to decide not to proceed further.

Clause 2 Crookes Healthcare was firmly of the opinion that it took all necessary steps to ensure that this scheme did not contravene any of the above mentioned clauses of the Code, and that the documentation provided to its staff and the doctors at the time demonstrated this clearly. Crookes Healthcare therefore believed that this scheme and its actions did not contravene Clause 2.

In summary, Crookes Healthcare took full account of the requirements of the Code. It was its firm belief that no breach of the Code had occurred.

PANEL RULING

The Panel noted that the Crookes Digital Dermatology Programme was set up in 2000. It had been examined by Crookes Healthcare in relation to the 1998 Code. The next edition of the Code had come into operation on 1 July 2001. The scheme had run for approximately one year and therefore would be covered by the 2001 Code.

The Panel noted that the territory manager who had visited the complainant to talk about the loan of the camera had left the company and therefore it was not possible to obtain his comments on the complaint. Crookes Healthcare had provided copies of the briefing material for the loan of the camera.

The Panel observed that it was difficult in such cases to know exactly what had transpired between the parties. A judgement had to be made on the evidence which was available bearing in mind that extreme dissatisfaction was usually necessary for a complaint to be made.

The Panel noted that the loan agreement stated that 'I will select patients with psoriasis who I feel are suitable for treatment with a vitamin D_3 analogue and for whom, in my clinical judgement and discretion, I feel Curatoderm would be the appropriate therapy to prescribe'. The loan agreement referred to the doctor being free to use the camera for other clinical purposes during the period of the loan but SmartMedia cards supplied by Crookes Healthcare could not be used for such other purposes.

The loan agreement stated that the photographs could appear in professional journals, textbooks or be used in Crookes Healthcare's promotional material. The company response referred to the photographs appearing only in promotional material.

The Clinician Briefing Document stated that patients to be photographed were those that the clinician felt were suitable for treatment with a vitamin D_3 analogue and were suitable for treatment with Curatoderm. Similar information was given in the Territory Manager Briefing Document. The Clinician Briefing Document also stated that the prescription of any Crookes Healthcare's product was entirely at the discretion of the clinician and the loan of a camera to record dermatological conditions was in no way provided in exchange for the prescription of Crookes Healthcare's product. This was not included in the Territory Manager Briefing Document.

The instructions to invite a clinician to join the programme included a list of questions in order that the most appropriate clinicians could be selected. These started with questions to establish their interest in dermatology and then whether they influenced the PCG/PCT formulary and whether they had some experience of Curatoderm or was it a new product to them.

A flow chart set out a step-by-step guide. This included a section 'Clinician identifies patients suitable for vitamin D_3 treatment and suitable for treatment with Curatoderm'.

The Panel considered that it was reasonable for Crookes Healthcare to try to obtain photographs of dermatological conditions and it would be useful for the company to have 'before and after' photographs of patients prescribed Curatoderm. The means of obtaining such photographs had to comply with the Code.

Clause 18.1 stated that no gift, benefit in kind or pecuniary advantage should be offered or given as an inducement to prescribe, supply, administer, recommend or buy any medicine subject to the requirements of Clause 18.2. Gifts in the form of promotional aids were allowed provided they were inexpensive and relevant to the practice of the recipient's profession or employment. The supplementary information to Clause 18.1 stated that items provided for long term loan were regarded as gifts.

The digital camera in question was not a gift. It was provided on loan but not on long term loan. Crookes Healthcare had asked for the cameras to be returned and this has been referred to in the loan agreement.

The Panel considered that the loan of the camera might be seen as a pecuniary advantage but if recipients wanted to use the camera for other clinical

purposes then they had to purchase their own SmartMedia cards as set out in the loan agreement. The key question was whether the loan of the camera amounted to an inducement to prescribe. The documentation stated that patients to be photographed were to be those the clinicians felt were suitable for treatment with a vitamin D_3 analogue and suitable for treatment with Curatoderm. No payments of any sort were made.

The complainant alleged that the representative expected the complainant to prescribe and to continue to prescribe Curatoderm for patients to be photographed. Crookes Healthcare had not been able to respond to this point as the representative had left the company. In the Panel's view the briefing material was on the limits of acceptability and could have been made clearer by repeating the information in the Clinician Briefing Document that the loan of the camera was in no way provided in exchange for the prescription of the Crookes Healthcare's product. The briefing material had not sufficiently addressed the issue of avoiding any impression that the loan of the camera was linked to the prescribing of Curatoderm.

On balance the Panel did not consider that the briefing material was such that it instructed representatives that the loan of the camera was conditional on the prescribing of Curatoderm. Taking all the factors into account the Panel decided that, on balance, the arrangements for the loan of the camera were not unacceptable. It was impossible to know what had been said by the representative to the complainant. The representative had left the company and had not therefore been able to put forward his version of events. There was no evidence that the representative had used the offer of the loan of the camera as an inducement to gain an interview. The Panel ruled no breach of Clauses 2, 9.1, 15.2, 15.3 and 18.1 of the Code.

Complaint received **4 April 2002**

Case completed **7 June 2002**

CASE AUTH/1296/4/02

CONSULTANT PSYCHIATRIST v PFIZER

Advertisement to the public

A consultant psychiatrist complained about a Pfizer advertisement which had appeared in The Observer Magazine with the headline '1 in 10 men has erection problems but no one likes to talk about it', adjacent to a photograph of a man and woman. The advertisement bore the logos of The Impotence Association and The Men's Health Forum. The Pfizer logo appeared beneath the photograph immediately after the statement 'The first step to a better love life'. The complainant alleged that the advertisement constituted direct advertising to the public.

The Panel did not consider that the advertisement constituted an advertisement to the general public for a prescription only medicine; no breach of the Code was ruled in that regard.

The Panel noted that the Pfizer company logo appeared in a highlighted box at the bottom of the photograph, immediately after and in the same line of text as the statement 'The first step to a better love life'. The Panel considered that within the context of an advertisement which encouraged patients to seek advice and treatment on erectile dysfunction, the juxtaposing of the company name adjacent to the aforementioned statement implied that a Pfizer product might be the first step to a better love life. On balance the Panel considered that the advertisement would encourage patients to ask their doctors specifically for the Pfizer product which would in effect amount to asking for a prescription for Viagra. The Panel considered that the advertisement thus would encourage patients to ask their doctors to prescribe a specific product. A breach of the Code was ruled.

A consultant psychiatrist complained about an advertisement from Pfizer Limited which had appeared in The Observer Magazine, 31 March.

The advertisement had the headline '1 in 10 men has erection problems but no one likes to talk about it', adjacent to a photograph of a man and woman. Text beneath stated:

'Erection problems don't just affect your sex life. They can affect all areas of your life. And the most difficult thing of all is talking about it. Especially to your partner.

It may help to know that you're not alone. 1 in 10 men experience this common medical condition at some time in their lives. And most of them could be managed effectively with appropriate treatment options.

Asking for help isn't easy. But you can do something now. Call us for a free, confidential information pack explaining the causes and treatment of erection problems, and how to talk to your doctor about it. Don't suffer in silence. Take the first step today.'

This was followed by a telephone number and a website address. A coupon appeared in the bottom right-hand corner of the advertisement by which the reader could request more information. A reply paid card was also attached to the advertisement.

The advertisement bore the logos of The Impotence Association and The Men's Health Forum. The Pfizer logo appeared beneath the photograph immediately after the statement 'The first step to a better love life'.

Pfizer marketed Viagra.

COMPLAINT

The complainant alleged that the advertisement constituted direct advertising to the public which he understood was prohibited.

When writing to Pfizer the Authority asked it to respond in relation to the requirements of Clauses 20.1 and 20.2 of the Code. The Authority drew Pfizer's attention to an earlier case, Case AUTH/1081/10/00, which had concerned a radio advertisement.

RESPONSE

Pfizer explained that erectile dysfunction was a distressing medical condition which could have a serious impact on a patient's psychological and social health as well as affecting their partner and the family unit. The Men's Health Forum and The Impotence Association (both of which were involved in the current campaign) stated that as many as 1 in 10 men in the UK were thought to suffer from this distressing condition.

Erectile dysfunction condition had long been seen as a taboo subject which the 'Understanding Impotence' campaign in 2000 sought to address. The advertisement in question formed part of an updated campaign to further erode the taboo and to encourage men to seek treatment for their condition. Erectile dysfunction could also be a marker of more serious conditions, such as diabetes, high blood pressure, cardiovascular disease and depression.

The advertisement concerned was one of two similar advertisements which had been used. The reason for this was that the advertisement was intended to raise awareness in both men with erection problems and their partners, with the aim of encouraging the men to visit their doctor. The picture on the two advertisements and the layout was the same, the only substantive difference was that the copy in the advertisement which was included in publications which were aimed at women differed slightly to suit the audience to which it was directed.

A reply paid card was included in some of the advertisements. It was called a 'tip on' and was supposed to increase response rates over coupons which people had to cut out and put in an envelope. People who responded to the advertisement received a booklet called 'Understanding Erection Problems – A Few of Your Questions Answered' and an Impotence Association/Men's Health Forum questionnaire on erectile dysfunction.

The Authority had requested details of the differences between the materials sent to respondents and those sent during the 'Understanding Impotence' campaign which was considered in Case AUTH/1081/10/00. Briefly the existing materials were based on the 'Understanding Impotence' campaign materials but they had been updated.

In the 'Understanding Erection Problems – A Few of Your Questions Answered' booklet, the section, 'Your Treatment Options', discussed the various treatment options available. Pfizer did not believe that oral treatments were accorded undue preference and indeed in terms of location and amount of words used, therapy, constriction devices, intracavernosal injections and transurethral therapy all got higher priority. Viagra was not the only oral treatment now available. The item was factual rather than promotional and it stated that 'Not every treatment will work for you …' and 'Your Doctor will be able to help explain the best option for you'. This section, in accordance with the aim of the campaign in general, put the emphasis on talking to a doctor.

The section 'Talking to Your Doctor', merely encouraged men to go to see their doctor and reassured them that GPs and practice nurses were used to discussing erection problems. It was also suggested that men should consider visiting their GP with their partner because of the effect that such problems could have on relationships. It did not suggest asking for any particular treatment.

Pfizer submitted that there had been no breach of Clause 20.1. Viagra was not mentioned anywhere in the advertisement. The advertisement did not even mention medicines. It mentioned 'treatment options' and there were many treatment options which a doctor might recommend to assist a patient presenting with erectile dysfunction. These options were presented in a factual manner in the booklet 'Understanding Erection Problems – A Few of Your Questions Answered'. Oral treatments were mentioned in the 'Your Treatment Options' section but Viagra was not the only oral treatment for erectile dysfunction.

With regard to Clause 20.2, Pfizer submitted that the advertisement and the associated materials did not breach this clause. No statement was made which encouraged patients to ask for a specific treatment. The aim of the advertisement was to encourage patients to go to see their doctors, discuss their condition and, where appropriate, the doctor could, using clinical judgement, determine the suitable treatment option.

PANEL RULING

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2 permitted information to be supplied directly or indirectly to the general public but such information had to be factual and provided 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 noted that the transcripts of two radio advertisements had been considered in Case AUTH/1081/10/00. The Panel had considered that the information provided, the radio advertisements, a telephone helpline and an information pack did not constitute advertising a prescription only medicine to the public nor would the information encourage patients to request a specific medicine. There was a fine distinction between education and promotion.

No breach of Clauses 20.1 and 20.2 of the Code was ruled.

Turning to the case now before it, Case AUTH/1296/4/02, the Panel considered that as the materials at issue were different to those previously at issue it was obliged to consider the new complaint.

The text to the advertisement at issue discussed erection problems and stated that '… most of them could be managed effectively with appropriate treatment options'. Readers were encouraged to request a free information pack which explained, *inter alia*, how to talk to their doctor. A telephone advice line, a website address and a reply paid card were provided. The information pack consisted of a covering letter, a questionnaire and a booklet. The covering letter was signed by the President of The Mens Health Forum and the Director of The Impotence Association and referred to the booklet and questionnaire. The questionnaire asked general questions about the patient's condition and treatment. The booklet referred to aspects of erection problems including the causes, common misunderstandings and treatment options. The booklet gave a list of useful contacts and what was the next step. In relation to treatment options there was a general description of sex and/or couple's therapy, vacuum constriction devices, intracavernosal injection therapy, transurethral therapy, oral treatments, hormone treatment, penile prosthesis and other surgical treatments. Each item in the mailing included the Pfizer logo and a statement 'Supported by an educational grant from Pfizer Limited'.

The Panel examined the advertisement in question. The Panel did not consider that it constituted an advertisement to the general public for a prescription only medicine. No breach of Clause 20.1 was thus ruled.

The Panel noted that the Pfizer company logo appeared in a highlighted box at the bottom of the photograph, immediately after and in the same line of text as the statement 'The first step to a better love life'. The Panel considered that within the context of an advertisement which encouraged patients to seek advice and treatment on erectile dysfunction the juxtaposing of the company name adjacent to the aforementioned statement, implied that a Pfizer product might be the first step to a better love life. On balance the Panel considered that the advertisement would encourage patients to ask their doctors specifically for a Pfizer product which would in effect amount to asking for a prescription for Viagra. The Panel considered that the advertisement thus would encourage patients to ask their doctors to prescribe a specific product. A breach of Clause 20.2 of the Code was ruled.

The Panel noted that the complaint was about the advertisement. There was no specific allegation about the information pack, the telephone helpline or the website. These must comply with the Code but were not considered by the Panel.

During its consideration of this case the Panel noted that the advertisement did not clearly state that it had been sponsored by Pfizer as required by Clause 9.9 of the Code. The Panel had similar concerns about the telephone helpline. The Panel requested that this be drawn to Pfizer's attention.

Complaint received **4 April 2002**

Case completed **17 May 2002**

CASE AUTH/1297/4/02

SCHERING-PLOUGH v AVENTIS PHARMA

Promotion of Telfast

Schering-Plough complained about the promotion of Telfast (fexofenadine) by Aventis Pharma. The materials at issue were a leavepiece, a mailing, a letter to pharmaceutical advisors headed 'Discontinuation of Clarityn (loratadine) – 3rd December 2001' and a letter headed 'IMPORTANT: Notice of prescription changes for allergy sufferers'.

The claims 'Telfast – Superior efficacy vs. loratadine' appeared on the leavepiece, 'Telfast has demonstrated superior efficacy over loratadine' appeared on the mailing, and 'Telfast has demonstrated superior efficacy vs loratadine' appeared in the letter to pharmaceutical advisors. In Schering-Plough's view the first claim stated directly, and the second strongly implied, that Telfast was more efficacious than loratadine. This was not so as of the two studies comparing the efficacy of fexofenadine and loratadine, one was clearly in favour of loratadine (Prenner *et al*) and one was possibly in favour of fexofenadine (Van Cauwenberge *et al*). The evidence could not support a claim of superiority of fexofenadine over loratadine.

The Panel noted that Van Cauwenberge compared fexofenadine, loratadine and placebo in the treatment of seasonal allergic rhinitis. In the assessment of overall effectiveness of medication there was no significant difference between the treatment groups. The Panel considered that the study did demonstrate advantages for Telfast over loratadine with regard to some parameters but it did not show that overall Telfast was superior to loratadine as implied by the claims at issue. The Panel considered that all three claims were misleading and unfair. Breaches of the Code were ruled.

Schering-Plough noted that there were two doses of Telfast, 120mg for hayfever and 180mg for urticaria. Using desloratadine as a comparator, the 120mg dose of Telfast was cheaper, the 180mg dose was more expensive. In spite of this the Aventis material implied that Telfast was always cheaper then desloratadine.

Schering-Plough considered that in Aventis' letter to pharmacists advising them that patients would soon be presenting prescriptions for Telfast the claim '… Telfast offers allergy sufferers fast effective relief from allergy symptoms whilst being less expensive than NeoClarityn, Zirtek and Xyzal', without qualification, was inaccurate. Furthermore, the mailing stated that 'Telfast gives fast and lasting relief to your budget', followed by a bullet point 'What the NHS saves when a patient is changed to Telfast' which was followed by a list of savings when a patient switched to Telfast. In view of the prominence of the previous statements as well as the fact that the mailing referred to the indications of both hayfever and urticaria, Schering-Plough believed that the overall effect was that Telfast was a less expensive antihistamine which was inaccurate.

The Panel noted its observation in the previous case, Case AUTH/1273/2/02, that changing patients from desloratadine, loratadine, cetirizine or levocetirizine to Telfast 180 for urticaria would increase prescribing costs. The Panel had considered that the mailing was misleading and a breach of the Code was ruled.

Turning to the case now before it the Panel considered that the ruling in the previous case also applied to Schering-Plough's complaint about the mailing. Breaches of the Code were ruled as alleged. With regard to the letter headed 'Important: Notice of prescription changes for allergy sufferers', the Panel considered that the impression given was that both doses of Telfast were less expensive than NeoClarityn, Zirtek and Xyzal. This was not so as acknowledged by Aventis. The Panel ruled breaches of the Code as alleged.

Schering-Plough Ltd submitted a complaint about the promotion of Telfast (fexofenadine) by Aventis Pharma Ltd.

The materials at issue were a two page leavepiece (ref TEL050101), a two page mailing (ref TEL1281201), a letter to pharmaceutical advisors headed 'Discontinuation of Clarityn (loratadine) – 3rd December 2001' (ref TEL 0900901) dated 28 September, signed by a medical advisor and a product manager and a letter headed 'IMPORTANT: Notice of prescription changes for allergy sufferers'.

1 Claims 'Telfast – Superior efficacy vs. loratadine', 'Telfast has demonstrated superior efficacy over loratadine' and 'Telfast has demonstrated superior efficacy vs loratadine'

The first claim appeared on the leavepiece. The second claim appeared on the mailing and was referenced to Van Cauwenberge *et al* (2000). The third claim appeared in the letter to pharmaceutical advisors.

COMPLAINT

In Schering-Plough's view the first claim stated directly, and the second strongly implied that Telfast was more efficacious than loratadine. This was not so. Each claim was alleged to be in breach of Clauses 7.2 and 7.3 of the Code.

Schering-Plough stated that there were two published studies comparing the efficacy of fexofenadine and loratadine. One was clearly in favour of loratadine, one possibly in favour of fexofenadine. The evidence could not support a claim of superiority of fexofenadine over loratadine.

In Prenner *et al* 2000 with 509 subjects, loratadine was demonstrated to have greater efficacy than fexofenadine in the primary endpoint. In Van Cauwenberge *et al* 2000 with 639 patients, there was no difference between fexofenadine and loratadine in the primary efficacy parameter, and a superiority of fexofenadine over loratadine in only 3 of the secondary efficacy parameters. It was difficult to see how Aventis could conclude from these two studies that the comparison was accurate, balanced, fair or

objective. Schering-Plough's view was that, at the very least, the issue of superiority of one antihistamine over another was not yet proven. The claims should reflect this.

Furthermore, the claim 'Telfast – Superior efficacy vs. loratadine' in the leavepiece appeared to be supported by reference to three publications (Mösges and Van Cauwenberge 2000; Howarth 2000; Van Cauwenberge). However, an examination of these papers showed them all to be commentaries on the same study. Schering-Plough stated that this was a case of triple rather than 'double-dipping', which had the effect of misleading the reader as to the weight of evidence behind the claims.

Schering-Plough was particularly concerned about Aventis' use of the claims as it went against a commitment Aventis made in July 2001 not to make this claim, a commitment that resulted, at that time, in Schering-Plough withdrawing a complaint made to the Authority against Aventis.

RESPONSE

Aventis noted that the leavepiece was prepared in January 2001, and, following communication with Schering-Plough, it had been withdrawn and had not been used promotionally since August 2001.

Aventis did not believe that the claim 'Telfast has demonstrated superior efficacy over loratadine' was in breach of the Code. The referenced study, Van Cauwenberge *et al* (n=680) compared the efficacy, safety and impact on quality of life in seasonal allergic rhinitis patients of fexofenadine and loratadine. Fexofenadine was significantly more effective than loratadine in relieving itchy, watery red eye symptoms and nasal congestion, the main symptoms of hayfever. Loratadine was not significantly different from placebo with regard to nasal congestion. In addition, fexofenadine was significantly better than loratadine in improving patients' quality of life which was recognised as an important goal in the management of patients with seasonal allergic rhinitis [hayfever]. Therefore the claim 'Telfast has demonstrated superior efficacy over loratadine' was entirely correct.

The patients in Prenner *et al* had already failed therapy with another antihistamine. This was a very specific and different patient population. Aventis had not claimed that Telfast was superior in treatment resistant patients.

This claim was used in the mailer which had been the subject of a previous case, Case AUTH/1273/2/02; the findings of the Panel in this case were documented in a letter to Aventis on 11 March 2002. To summarise, the ruling on this piece was that Aventis was in breach with respect to the cost comparison. Aventis had already withdrawn the material due to another case considered by the Panel. The material had not been subsequently used in any promotional activities by Aventis.

Therefore Aventis submitted that it was not in breach of Clauses 7.2 and 7.3 of the Code.

Schering-Plough had also stated that the claim was also found in an unreferenced promotional circular from the Telfast Product Manager and Medical Advisor. Aventis stated that the letter was in fact a targeted mailing to pharmaceutical advisors (ref TEL0900901) and not a circular, which was sent out only once, in October 2001. In addition, this letter was clearly referenced and contained the prescribing information in accordance with the Code.

PANEL RULING

The Panel noted that Schering-Plough was incorrect with regard to the references in the leavepiece. The claim in question 'Telfast – Superior efficacy vs. loratadine' was not referenced. The claim that followed was referenced to the studies quoted by Schering-Plough.

The Panel noted that the study by Van Cauwenberge *et al* compared fexofenadine 120mg, loratadine 10mg and placebo in the treatment of seasonal allergic rhinitis. The total symptom score was the sum of four individual scores these being sneezing, rhinorrhea, itchy nose, palate and/or throat and itchy, watery and/or red eyes. Nasal congestion was also evaluated. The primary efficacy parameter was the change in the mean 24 hour reflective total symptom score during the double blind treatment period from that during the baseline period. In the assessment of overall effectiveness of study medication there was no significant difference between the treatment groups. Fexofenadine was significantly better at improving 24 hour reflective itchy/watery/red eyes and nasal congestion than loratadine ($p \leq 0.05$ for both). Improvement of quality of life in the fexofenadine treated group was significantly greater than in the loratadine treated group($p \leq 0.03$). The differences in scores between fexofenadine and loratadine were smaller than the smallest difference that could be considered clinically important. The authors argued that using numbers needed to treat supported the clinical relevance of fexofenadine in improving quality of life.

The Panel considered that the study did demonstrate advantages for Telfast over loratadine with regard to some parameters. The study did not show that overall Telfast was superior to loratadine as implied by the claims at issue. The Panel considered that all three claims were misleading and unfair. Breaches of Clauses 7.2 and 7.3 of the Code were ruled.

2 Cost Comparisons

COMPLAINT

Schering-Plough noted that there were two doses of Telfast, 120mg and 180mg, the 120mg dose was licensed for hayfever, the 180mg was licensed for urticaria. Using desloratadine (or the other antihistamines listed) as a comparator, the 120mg dose of Telfast was cheaper, the 180mg dose was more expensive. In spite of this the Aventis material implied that Telfast was always cheaper then desloratadine. Schering-Plough alleged breaches of Clauses 7.2 and 7.3.

While Schering-Plough was pleased that Aventis had agreed to withdraw a letter to practice staff stating 'I

am also reliably informed that it [Telfast] is less expensive than NeoClarityn …' it was unfortunate that Aventis had declined to remove other instances of this claim. For example, in a letter to pharmacists headed 'Notification of Prescription Change. Please be aware that, due to a practice review, patients will soon be presenting prescriptions for Telfast 120mg and Telfast 180mg (fexofenadine)', the second paragraph stated '… Telfast offers allergy sufferers fast effective relief from allergy symptoms whilst being less expensive than NeoClarityn, Zirtek and Xyzal'. Without qualification, and there was none, the claim was clearly inaccurate. Schering-Plough alleged a breach of Clause 7.2.

Furthermore, the mailing stated that 'Telfast gives fast and lasting relief to your budget', followed by a bullet point 'What the NHS saves when a patient is changed to Telfast' which was followed by a list of purported savings when a patient was switched from the most popular antihistamines to Telfast. The bullet point was linked by an asterisk to the footnote, that the price comparison only referred to Telfast 120. However, in view of the prominence of the previous statements as well as the fact that the mailing referred to the indications of both hayfever and urticaria, Schering-Plough believed that the overall effect was that Telfast was a less expensive antihistamine generally, a claim which was in breach of Clause 7.2.

RESPONSE

Aventis stated that at no point had it made a claim that Telfast was cheaper than other antihistamines.

In light of the ruling by the Panel in Case AUTH/1273/2/02 the mailing, was no longer in use.

The other item the complainant referred to was not a circular to pharmacists, rather a letter provided within a pack provided for the GP to issue to the pharmacist if they wished. While Telfast 120mg was less expensive than NeoClarityn, Aventis accepted that this item also made reference to Telfast 180mg where this was not so. Aventis accepted this error and would withdraw the material with immediate effect.

PANEL RULING

The Panel noted its observation in the previous case, Case AUTH/1273/2/02, that with one exception all of the claims on the mailing appeared to relate to Telfast 120; however the last bullet point beneath the claim 'Telfast provides fast and lasting relief of hayfever symptoms' read 'Telfast 180 provides fast relief of urticaria' thus introducing the other presentation. This was immediately followed by the claim 'Telfast gives fast and lasting relief to your budget'. Given that in this claim the presentation of Telfast had not been specified and that it was preceded by claims about hay fever and about urticaria, some readers might assume that the savings shown related to both Telfast 120 and Telfast 180 which was not so. The savings only related to the use of Telfast 120. Although this was stated in the footnote to the table the Panel noted that it was an accepted principle under the Code that otherwise misleading statements could not be qualified by the small print. The Panel noted that changing patients from desloratadine, loratadine, cetirizine or levocetirizine to Telfast 180 for urticaria would increase prescribing costs. The Panel considered that the mailing was misleading and a breach of Clause 7.2 was ruled.

Turning to the case now before it, Case AUTH/1297/4/02, the Panel considered that the ruling in the previous case also applied to Schering-Plough's complaint about the mailing. Breaches of Clauses 7.2 and 7.3 of the Code were ruled as alleged.

With regard to the letter headed 'Important: Notice of prescription changes for allergy sufferers', the Panel considered that the impression given was that both doses of Telfast were less expensive than NeoClarityn, Zirtek and Xyzal. This was not so as acknowledged by Aventis. The Panel ruled breaches of Clauses 7.2 and 7.3 as alleged.

The Panel did not consider the leavepiece nor the letter to practice staff as no specific complaint had been made about them by Schering-Plough.

Complaint received **8 April 2002**

Case completed **10 June 2002**

CASE AUTH/1301/4/02

PFIZER v GLAXOSMITHKLINE

Report in The Sun

Pfizer complained about comments reported to have been made by the chief executive officer of GlaxoSmithKline in The Sun newspaper under the headline 'Viagra for quickie sex is coming soon'.

The article stated:

'British drugs giant GlaxoSmithKline is launching its own souped-up version of sex drug Viagra.

Glaxo says the new product works faster than Viagra, made by American giant Pfizer. It will be launched in the US this year and will probably be in Britain next year.

Glaxo chief executive JP Garnier promised that the product, code-named Vardenafil, would have none of the side-effects of Viagra. He said some patients on Viagra had dizzy spells and blue flashes'.

He added 'Viagra can take up to an hour to work. The advantage of our product is that you won't have to wait so long. And with Viagra, some people who take it see the world coloured blue – but you won't have that problem with our drug'.

The chief executive officer was quoted as promising '…that the product code-named Vardenafil, would have none of the side-effects of Viagra. He said some patients on Viagra had dizzy spells and blue flashes'. Pfizer considered that this was highly misleading and implied that vardenafil was without side-effects. There had been no published studies comparing the side-effect profiles of the two medicines.

The chief executive officer was also quoted as saying 'Viagra can take up to an hour to work. The advantage of our product is that you won't have to wait so long'. Vardenafil did not have a UK marketing authorization and Pfizer considered this statement was promotional in nature as it was information to the general public. There had been no published clinical studies in man comparing the two medicines and so Pfizer viewed a comment such as this as unbalanced in nature and misleading.

Pfizer alleged that the comments made in this article were disparaging of Viagra and even if they were true were inappropriate for the target audience of readers of a national newspaper.

The Panel examined the transcript provided by GlaxoSmithKline which referred to vardenafil as the second generation Viagra '…Viagra Plus, because it has some of the advantages you would hope for in comparison to Viagra', which referred to expectations that the product was active faster so 'you do not have to wait so long' and 'It also is a very safe product'. Further, vardenafil was described as being exquisitely selective for the PDE5 receptor and not the PDE6 receptor. The impression given was that this would mean vardenafil would not produce the visual disturbances associated with Viagra.

The Panel considered that the transcript did not present the information in a balanced way. The Panel was extremely concerned that vardenafil had been described as a 'very safe product'. With regard to speed of onset of action the data provided by GlaxoSmithKline referred to pharmacokinetic studies. The transcript stated that 'We expect the product is active faster, so you do not have to wait as long'. Pfizer had stated that there were no published clinical studies comparing the two products. The Panel considered that the transcript was not balanced and by referring to vardenafil as 'very safe' it was misleading with respect to the safety of the product. The Panel ruled a breach of the Code.

The Panel did not consider that the transcript disparaged Viagra and no breach of the Code was ruled in that regard.

Pfizer Limited complained about comments reported to have been made by Dr J P Garnier, the chief executive officer of GlaxoSmithKline. The comments had been reported in The Sun newspaper on 15 February under the headline 'Viagra for quickie sex is coming soon'.

The article stated:

'British drugs giant GlaxoSmithKline is launching its own souped-up version of sex drug Viagra.

Glaxo says the new product works faster than Viagra, made by American giant Pfizer. It will be launched in the US this year and will probably be in Britain next year.

Glaxo chief executive JP Garnier promised that the product, code-named Vardenafil, would have none of the side-effects of Viagra. He said some patients on Viagra had dizzy spells and blue flashes.

He added 'Viagra can take up to an hour to work. The advantage of our product is that you won't have to wait so long. 'And with Viagra, some people who take it see the world coloured blue – but you won't have that problem with our drug'.

COMPLAINT

Pfizer stated that the article contained alleged quotes about vardenafil, a GlaxoSmithKline/Bayer alliance product in development, and Pfizer's product Viagra (sildenafil).

Pfizer believed that a number of statements in the article were promotional in nature, disparaging of Viagra and inappropriate coming from the chief executive officer of a pharmaceutical company. Pfizer's medical director wrote to the medical director of GlaxoSmithKline expressing Pfizer's concern and requesting a prompt explanation. Pfizer also requested a copy of the press briefing materials and details of any steps taken to rectify the situation.

Pfizer received a reply in which GlaxoSmithKline requested a copy of the article prior to a response. This surprised Pfizer, as it would have thought that a company of the size of GlaxoSmithKline would have

knowledge of press materials relating to its products. Pfizer supplied the article and received a subsequent letter which stated that GlaxoSmithKline was unsure as to Pfizer's concerns and which breaches of the Code it believed to have occurred.

Pfizer therefore complained under Clauses 7.9, 8.1 and 20.2 of the Code.

Dr Garnier was quoted as promising '…that the product code-named Vardenafil, would have none of the side-effects of Viagra. He said some patients on Viagra had dizzy spells and blue flashes'. This was highly misleading and implied that vardenafil was without side-effects. There had been no published studies comparing the side-effect profiles of the two medicines. Furthermore data presented by Bayer at a number of scientific congresses would suggest that the side-effect profile was very similar to that of Viagra, including visual disturbances at higher doses.

Elsewhere Dr Garnier was quoted as saying 'Viagra can take up to an hour to work. The advantage of our product is that you won't have to wait so long'. Vardenafil did not have a UK marketing authorization and this statement was clearly promotional in nature as it was information clearly to the general public.

There had been no published clinical studies in man comparing the two medicines and so Pfizer viewed a comment such as this as unbalanced in nature and misleading. Furthermore, in a study conducted by Bayer Pharmaceuticals in a rabbit model comparing the two medicines, the time of onset was in fact similar. The claim was alleged to be exaggerated.

Pfizer alleged that the comments made in this article were disparaging of Viagra and even if they were true were inappropriate for the target audience of readers of a national newspaper.

RESPONSE

GlaxoSmithKline stated that the article was reporting on a financial presentation by Dr J P Garnier, chief executive officer of GlaxoSmithKline, conducted on 14 February. GlaxoSmithKline refuted the allegations of breaches of the Code.

GlaxoSmithKline explained that vardenafil was a selective PDE5 inhibitor which had been filed in the EU through a centralised procedure in December 2001 for the treatment of erectile dysfunction. It currently did not have marketing authorization in any country. GlaxoSmithKline and Bayer were global co-marketing partners for vardenafil in every country other than Japan. Both companies would be involved in the sales and marketing of the product.

Dr Garnier had presented a briefing to financial correspondents for the 2001 year-end results for GlaxoSmithKline. Sales and other financial data were presented as well as an overview of future potential from pipeline products. Dr Garnier had no further discussions with reporters following the briefing and therefore the transcript could be considered a full and accurate account of what was said. A copy of the transcript was provided.

Dr Garnier did not state that vardenafil would have none of the side-effects of Viagra. The only side-effects that he referred to were visual disturbances associated with Viagra such as 'seeing the world in blue'. It was well known that Viagra caused visual side-effects. Altered vision was reported in the summary of product characteristics (SPC). Visual disturbance was widely believed to occur due to inhibition of phosphodiesterase isoenzyme type 6 which was present in the retina. As well as inhibiting the type 5 isoenzyme, Viagra also had an affinity for other subtypes, one of which was the type 6 isoenzyme.

In vitro studies had shown that vardenafil was approximately 10 times more potent than sildenafil at inhibiting PDE5 isolated from human platelets (vardenafil IC_{50}=0.7nM; sildenafil IC_{50}=6.6nM). With respect to the retinal isoform, vardenafil inhibited PDE6 with an IC_{50} PDE6 of 11nM compared to an IC_{50} of 49 for sildenafil: with reference to PDE5 this resulted in a selectively ratio of 15.7 for vardenafil compared to 7.4 for sildenafil.

Due to the superior selectivity of PDE5 over PDE6 of vardenafil compared to sildenafil, GlaxoSmithKline submitted that Dr Garnier's comments as in the transcript were not in breach of Clause 7.9.

GlaxoSmithKline believed that Clause 8.1 had not been breached. In the context of the meeting, which was financial, Dr Garnier was not in any way intending to disparage either Viagra or Pfizer. There were no disparaging references within the transcript to the product or the company.

GlaxoSmithKline did not believe that Clause 20.2 had been breached. The article quoted Dr Garnier as saying 'Viagra can take up to an hour to work. The advantage of our product is that you won't have to wait so long'. His actual statement was 'We expect the product is active faster so you do not have to wait so long. With Viagra it is an hour or so, I understand, but with vardenafil, it is supposed to be half an hour or less'.

Pharmacokinetic studies of vardenafil asserted a mean T_{max} of 0.6 hours in men with erectile dysfunction under 45 years of age and 0.5 hours in those over 65. Studies by Pfizer on the pharmacokinetics of sildenafil had demonstrated a mean T_{max} of approximately 1 hour. As such the statement 'we expect the product is active faster…' GlaxoSmithKline believed to be balanced and fair.

GlaxoSmithKline stated that with reference to the transcript and the fact that the presentation was to a closed invited group of financial journalists, it considered that there had been no breaches of the Code as alleged by Pfizer.

PANEL RULING

The Panel noted that GlaxoSmithKline and Bayer were to co-market vardenafil. The complaint concerned comments made by GlaxoSmithKline at a financial briefing for its 2001 year end results; in the circumstances the matter was only taken up with that company.

The Panel noted that Clause 20.2 of the Code permitted information about medicines to be made available to the public provided, *inter alia*, it was

'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'. It further noted that the supplementary information to Clause 20.2, Financial Information, stated that 'Information made available in order to inform shareholders, the Stock Exchange and the like by way of annual reports and announcements etc. may relate to both existing medicines and those not yet marketed. Such information must be factual and presented in a balanced way'.

The Panel noted that the article was reporting on a financial presentation made by the chief executive officer of GlaxoSmithKline.

The Panel examined the transcript provided by GlaxoSmithKline which referred to vardenafil as the second generation Viagra '…Viagra Plus, because it has some of the advantages you would hope for in comparison to Viagra'. The transcript referred to expectations that the product was active faster so 'you do not have to wait so long' and 'It also is a very safe product'. Further, vardenafil was described as being exquisitely selective for the PDE5 receptor and not the PDE6 receptor. The impression given was that this would mean vardenafil would not produce the visual disturbances associated with Viagra.

The Panel considered that the transcript did not present the information in a balanced way. It therefore did not meet the guidance in the supplementary information to Clause 20.2 of the Code in relation to financial information.

The Panel was extremely concerned that vardenafil had been described as a 'very safe product'. With regard to speed of onset of action the data provided by GlaxoSmithKline referred to pharmacokinetic studies. The transcript stated that 'We expect the product is active faster, so you do not have to wait as long'. Pfizer had stated that there were no published clinical studies comparing the two products. The Panel considered that the transcript was not balanced and by referring to vardenafil as 'very safe it was misleading with respect to the safety of the product. The Panel ruled a breach of Clause 20.2 of the Code. The Panel considered that the alleged breach of Clause 7.9 of the Code was covered by this ruling.

The Panel did not consider that the transcript disparaged Viagra and no breach of Clause 8.1 of the Code was ruled. Critical references to another company's product were acceptable under the Code provided that they were accurate, balanced, fair, etc, and could be substantiated.

Complaint received **19 April 2002**

Case completed **7 June 2002**

GENERAL PRACTITIONER v NOVARTIS

Advertisement to the public

A general practitioner complained about an advertisement in The Independent which featured a close up photograph of someone's toes with an arrow pointing to the big toe stating 'This little piggy's … infecting the rest of the family'. The advertisement referred to Stepwise which was sponsored by Novartis. Text beneath the photograph stated 'Discoloured, thick or brittle nails could mean you are one of the million or more people in the UK with fungal nail infection. The infection can spread to other parts of your body and to other people and won't go away without effective treatment from your GP. To find out what you should do next send for our free 12-page booklet all about feet and nails, by writing to STEPWISE, …'. Those interested could apply by Freepost, Freephone or the Internet. A logo stated 'Your first step towards healthier looking nails. Stepwise. Sponsored by Novartis'.

The complainant alleged that the advertisement was untrue as his understanding of fungal infections of nails was that they were often self-limiting and resolved spontaneously within a year, and thus it was inaccurate to say that 'the infection … won't go away without effective treatment from your GP'.

The Panel noted that the advertisement in question stated that fungal nail infection '… won't go away without effective treatment from your GP'. Several references had been provided by Novartis to substantiate this claim. The Panel considered that the statement in the advertisement was not unreasonable. It was a factual statement and no breach of the Code was ruled.

The Panel noted that the advertisement offered readers a free booklet about feet and nails which could be requested by writing, calling a Freephone number or via the Stepwise website. The Freephone helpline explained the nature of fungal nail infections and informed the caller that the fungus was unlikely to go away without treatment. The Stepwise website stated that the infection 'won't go away on its own' and the booklet stated 'The fungus won't go away without treatment'. The Panel considered that these statements were not unreasonable. They were factual statements covered by the Panel's ruling of no breach of the Code above.

A general practitioner complained to the British Institute of Regulatory Affairs Limited (BIRA) about an advertisement in The Independent, 17 April 2002. BIRA forwarded the GP's letter to the Authority.

The advertisement featured a close up photograph of someone's toes with an arrow pointing to the big toe stating 'This little piggy's … infecting the rest of the family'. The advertisement referred to Stepwise which was sponsored by Novartis Pharmaceuticals UK Ltd.

Text beneath the photograph stated 'Discoloured, thick or brittle nails could mean you are one of the million or more people in the UK with fungal nail infection. The infection can spread to other parts of your body and to other people and won't go away without effective treatment from your GP. To find out what you should do next send for our free 12-page booklet all about feet and nails, by writing to STEPWISE, …'. Those interested could apply by Freepost, Freephone or the Internet. A logo stated 'Your first step towards healthier looking nails. Stepwise. Sponsored by Novartis'.

COMPLAINT

The complainant alleged that the advertisement was untrue on a point of fact; his understanding of fungal infections of nails was that they were often self-limiting and resolved spontaneously within a year, and thus it was inaccurate to say that 'the infection … won't go away without effective treatment from your GP'. As this advertisement was misleading, the complainant felt that it should be withdrawn.

* * * * *

When writing to Novartis, the Authority reminded it that there had been a number of previous cases about the Stepwise campaign (Cases AUTH/313/6/95, AUTH/458/8/96, AUTH/516/3/97 and AUTH/1058/7/00). Case AUTH/1058/7/00 had concerned an allegation that claims that 'the fungus won't go away without treatment' and 'it is likely to get worse without treatment' might not be entirely true. The Panel had ruled no breach of Clause 20.2 of the Code as it considered the claims were not unreasonable. This ruling had not been appealed.

Paragraph 5.1 of the Constitution and Procedure stated that if a complaint concerned a matter closely similar to one which had been the subject of a previous adjudication it might be allowed to proceed at the discretion of the Director of the Authority if new evidence was produced by the complainant. Further, the Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Panel which was not the subject of an appeal to the Appeal Board. As no appeal had been made in Case AUTH/1058/7/00, this complaint was allowed to proceed.

* * * * *

RESPONSE

Novartis provided a number of publications which it submitted refuted the complainant's argument that nail infections were self-limiting and resolved spontaneously within a year. It was clear from a review of the literature on the subject of fungal nail infection that appropriate and accurate diagnosis of fungal involvement was essential as a basis for instigating treatment of fungal nail infection. It was equally clear, however, that spontaneous resolution of true fungal nail infections rarely if ever occurred.

Failure to appropriately treat such infections could lead to increasing cosmetic and functional disability for the infected individual, as well as contributing to the infectious pool for cross infection between individuals.

It should be remembered that people who chose to respond to the Stepwise advertisement were likely to have already identified that they had some concerns about nail infection, possibly fungal, and were seeking advice and guidance on how to manage it. They might well have noted for themselves a progression of their athletes foot or noted a gradual deterioration of their nails as a fungal infection spread and the nail changed colour and crumbled.

Although fungal infections of the nails might sometimes be incorrectly disregarded as superficial or cosmetic, it would be wrong to underestimate the implications of fungal nail infection to the patient or the eventual consequences of onychomycosis which could become unsightly, embarrassing and occasionally disabling. It was clear that patients themselves did not consider such conditions as transient or superficial or they would not feel prompted to find out more about the Stepwise materials.

The Stepwise Programme was based on research indicating that there was a large untreated reservoir of patients in the community who did not recognise that they had a fungal infection or who had received ineffective therapy in the past which had led them to consider their condition untreatable. Fungal nail infection was thought to affect over a million patients in the UK at any one time, with an estimated 200,000 new patients each year. An analysis of such patients had shown that as with athletes foot, only a small percentage of patients with fungal nail infection sought professional advice, although 80% felt that they would have done so if they had realised that they were suffering from a treatable fungal infection.

Novartis did not agree therefore that this statement in the advertisement was inaccurate or misleading. In addition, it should be emphasised that the Stepwise materials had been well received by the public since their introduction in 1995 as a useful source of disease awareness advice, in line with Clause 20.2 of the Code.

In conclusion, Novartis was confident that the Stepwise Programme materials including the advertisement in question were factual and balanced and continued to offer valuable guidance to patients who believed that they might have a fungal infection of their feet or nails. Novartis provided copies of the Stepwise booklet referred to in the advertisement, which would be sent out in response to a patient replying to the advertisement.

In answer to the Authority's request for clarification regarding the treatment options available to the general practitioner in relation to fungal nail infection, Novartis listed these in an appendix to its response.

PANEL RULING

The Panel considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake provided that such programmes were in accordance with the Code. Such activities might facilitate the market development of the sponsoring company's products but this was not necessarily in breach of the Code. Each case would need to be judged on its merits.

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines and certain other medicines to the general public. Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The advertisement in question stated that fungal nail infection '… won't go away without effective treatment from your GP'. Several references had been provided by Novartis to substantiate this, for example '… the well-documented lack of spontaneous remission totally invalidates any wait and watch policy' (Roberts 1999); 'Treating onychomycoses is difficult but it is important because they do not resolve spontaneously' (Denning *et al* 1995) and 'The disease rarely resolves spontaneously and recurrence after treatment is common' (Piérard 1993). The Panel thus considered that the statement in the advertisement was not unreasonable. The Panel considered it was a factual statement; no breach of Clause 20.2 was ruled.

In addition to the content of such an advertisement, an important factor in determining its acceptability would be the nature of the materials provided to enquirers. In this particular instance the advertisement offered readers a free booklet about feet and nails. The booklet could be requested by writing, calling a Freephone number or via the Stepwise website. The Freephone helpline explained the nature of fungal nail infections and informed the caller that the fungus was unlikely to go away without treatment. The Stepwise website stated that the infection 'won't go away on its own' and the booklet stated 'The fungus won't go away without treatment'. The Panel thus considered that these statements were not unreasonable. The Panel considered that they were factual statements covered by its ruling of no breach of Clause 20.2 above.

Complaint received **19 April 2002**

Case completed **10 June 2002**

CASE AUTH/1307/4/02

PRIMARY CARE TRUST PHARMACEUTICAL ADVISOR v ROCHE

Promotion of MabThera

A pharmaceutical advisor at a primary care trust complained about a MabThera (rituximab) compact disc (CD) issued by Roche. The cover of the CD sleeve stated 'MabThera – endorsed by NICE' and the inside cover read 'The National Institute for Clinical Excellence (NICE) has recommended MabThera for the treatment of follicular lymphoma patients who are chemotherapy-resistant or chemotherapy-intolerant'. The complainant stated that NICE guidance suggested that there were considerable deficiencies or uncertainties about the clinical effectiveness of rituximab and it was extremely misleading to represent the guidance as an endorsement or recommendation.

The Panel considered that the CD sleeve was misleading. The claim '… endorsed by NICE' did not reflect the NICE guidance nor did the claim that it 'recommended MabThera for the treatment of follicular lymphoma patients who were chemotherapy-resistant or chemotherapy-intolerant'. The sleeve did not mention that NICE had recommended certain conditions on the use of MabThera ie that for last line treatment it was recommended only in the context of a prospective case series. The Panel considered that the CD sleeve had not adequately reflected the NICE guidance and was misleading in this regard; a breach of the Code was ruled.

The Panel noted that the CD gave more information about the NICE guidance but had still not adequately described it and was thus misleading. A further breach of the Code was ruled.

The Panel noted that neither the CD sleeve nor the CD itself actually quoted the NICE guidance and therefore the guidance had not been misquoted. No breach was ruled in that regard.

COMPLAINT

A pharmaceutical advisor at a primary care trust complained about a MabThera (rituximab) compact disc (CD) which he had received in the post from Roche Products Limited.

The cover of the CD sleeve stated 'MabThera – endorsed by NICE'. The inside cover read 'The National Institute for Clinical Excellence (NICE) has recommended MabThera for the treatment of follicular lymphoma patients who are chemotherapy-resistant or chemotherapy-intolerant'.

The complainant noted that the section on the CD entitled NICE guidance did not in fact contain NICE's guidance but instead repeated the previous sentence.

The complainant noted that NICE's guidance on rituximab (Technology Appraisal No 37, March 2002) read:

'1.1 The use of rituximab for third-line or subsequent-line, but not 'last line', treatment of patients with recurrent or refractory Stage III or IV follicular lymphoma is not recommended.

1.2 For last-line treatment, rituximab is recommended only in the context of a prospective case series. All patients for whom alternative therapies have been exhausted (that is, those who are either chemo-resistant or chemo-intolerant – see section 4.1.3) would be appropriate for inclusion in the case series on the basis that data are systematically collected to allow aggregation and analysis at a national level. The Institute's recommendations for data to be recorded for this case series are set out in paragraphs 7.2 and 7.3.'

The complainant stated that the guidance suggested that there were considerable deficiencies or uncertainties about the clinical effectiveness of rituximab and it was extremely misleading to represent the above guidance as an endorsement or recommendation. The complainant alleged that the CD and its contents were in breach of several sections of Clause 7 of the Code.

When writing to Roche the Authority asked it to respond in relation to the requirements of Clause 7.2 and 11.2 in addition to Clause 7 as stated by the complainant.

RESPONSE

Roche stated that it had a commitment to communicate accurate and factual information regarding clinical use of MabThera within its licensed indication. The CD was developed to help clinicians and NHS managers integrate MabThera into the management of follicular lymphoma. In addition Roche wished to communicate timely information about the NICE guidance.

However since the complaint related solely to the aspects of the mailer relating to NICE guidance the response addressed those aspects. It was also pertinent to point out that NICE only assessed the use of MabThera in follicular lymphoma.

In this regard, the communication aimed to resolve some of the potential confusion around the wording of the guidance. Roche was aware that some confusion existed following direct feedback from those clinicians who had been involved in the NICE submission process and who had reviewed the final guidance prior to its issue.

Roche quoted Sections 1.1 and 1.2 of the NICE guidance and submitted that Section 1.1 (containing a double negative) was potentially confusing, especially for those who were not familiar with the disease area. However, a legitimate interpretation was that although third and subsequent line treatment was not

recommended, last line treatment was. This was further expanded in section 1.2 which recommended that rituximab was used only in the context of a prospective case series. At the time of the guidance and of the CD communication, no such case series had been established. The CD made this fact clear and also stated that further information would be provided regarding the collection of the data, once the case series had been determined.

Roche submitted that the information, as set out in the CD, provided a clear and accurate summary of the NICE guidance:

Roche noted that the CD stated –

'NICE have recommended rituximab for the treatment of follicular lymphoma patients who are either chemo-resistant or chemo-intolerant' i.e. 'All patients for whom alternative therapies have been exhausted' to quote section 1.2 of the NICE guidance. The terms 'chemo-resistant/chemo-intolerant patients' meant the same as 'those for whom alternative therapies have been exhausted'. In addition last line therapy would include patients if chemo-intolerant as defined in section 4.1.3b of the guidance.

Roche also clearly provided information in the CD about the recommendation to collect routine data on new patients starting treatment, as detailed in the NICE guidance. Furthermore, Roche stated on the CD that additional information on the implementation and the current status of the prospective case series would be provided in due course. This included a statement about patient access to treatment prior to the case series being established. This was based on email correspondence from the NICE executive in response to Roche's request for clarification on this matter. This stated that the recommendation was not conditional on the formal arrangements for setting up the case series.

Roche noted that the complainant stated that it was misleading to represent the NICE guidance as 'an endorsement or a recommendation'. However, NICE did indeed 'recommend' the use of rituximab – as found in section 1.2, Appendix C – Patient Information.

Roche believed that the information contained in the CD was an accurate reflection of the NICE guidance and provided a comprehensive summary of that guidance. Furthermore, Roche was aware that all stakeholders had access to the NICE guidance at the NICE website, a link to this was provided on the CD. Roche therefore refuted the allegation that the information provided was in breach of Clause 7 or its sub-sections. Roche also denied any breach of Clause 11.2 and submitted that the CD accurately reflected the meaning of the NICE guidance.

The CD was mailed to hematologists, oncologists, and other relevant health professionals in April. This was a single mailing, and there were no plans to repeat it. In addition, the CD was also made available at the British Society of Hematology meeting, April 2002.

PANEL RULING

The CD was presented in a fold out sleeve the front cover of which stated 'MabThera-endorsed by NICE'. The inside front cover stated that NICE had '… recommended MabThera for the treatment of follicular lymphoma patients who are chemotherapy-resistant or chemotherapy-intolerant'. A statement at the bottom of the inside front cover read 'This CD-ROM is designed to help clinicians and NHS managers integrate MabThera into the management of NHL [non-Hodgkin's lymphoma] in accordance with NICE guidance'. The back cover of the sleeve stated that 'MabThera is the only licensed treatment in the management of NHL endorsed by NICE'.

The CD also included information about the NICE guidance and stated that it was based on information from the MabThera NICE submission. The CD repeated some of the claims on the sleeve and also stated that NICE recommended that routine data be gathered on new patients starting treatment. The Panel noted that following an enquiry from Roche, NICE had stated that the recommendation that new patients were offered rituximab was not conditional on the formal arrangements for a case series having been set up at the time that treatment was initiated.

The Panel noted the NICE guidance about the use of MabThera when all other treatment options had been exhausted.

The Panel considered that the CD sleeve was misleading. The claim '… endorsed by NICE' did not reflect the NICE guidance nor did the claim that it 'recommended MabThera for the treatment of follicular lymphoma patients who were chemotherapy-resistant or chemotherapy-intolerant'. The sleeve did not mention that NICE had recommended certain conditions on the use of MabThera ie that for last line treatment it was recommended only in the context of a prospective case series. The Panel noted the response from NICE that use of the product was not conditional on the formal arrangements for the case series having been established at the time treatment was initiated.

The Panel considered that the CD sleeve had not adequately reflected the NICE guidance and was misleading in this regard; a breach of Clause 7.2 of the Code was ruled.

The Panel noted that the CD gave more information about the NICE guidance but had still not adequately described it. One 'page' of the CD stated in successive bullet points 'New patients who are chemotherapy resistant or chemotherapy intolerant should be offered MabThera' and 'It is recommended that routine data be gathered on new patients starting treatment'. The Panel considered that there was an implication that NICE considered the collection of data to be optional whereas the guidance itself implied that it was requisite. A further breach of Clause 7.2 of the Code was ruled.

The Panel noted that neither the CD sleeve nor the CD itself actually quoted the NICE guidance. There could therefore be no breach of Clause 11.2 of the Code. The Panel ruled accordingly.

Complaint received **29 April 2002**

Case completed **28 June 2002**

CASE AUTH/1308/4/02

LEO v AVENTIS PHARMA

Clexane leavepiece

Leo complained about a four page leavepiece for Clexane (enoxaparin) issued by Aventis Pharma. The inside pages of the leavepiece were headed 'The only LMWH [low molecular weight heparin] licensed for the prevention and treatment of VTED in surgical and acutely ill medical patients'. Below this appeared a chart comparing the licensed indications for Clexane with dalteparin, tinzaparin (Leo's product, Innohep), certoparin and reviparin. The column headed 'Clexane' had ticks for all the licensed indications listed. The chart indicated that whilst tinzaparin was licensed for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) it was not licensed for the 'Treatment of VTE [venous thromboembolic disease] presenting as DVT, PE or both'.

Leo had written to Aventis and complained that it was misleading to suggest that a patient presenting with a DVT and a PE could not be treated with Innohep under the current marketing authorization and that the implication that Clexane had additional benefit over Innohep for VTED treatment was not true. Aventis had agreed that all future Clexane pieces would not use this misleading comparison.

Subsequently the leavepiece was used at a local hospital by an Aventis representative. Leo stated that Aventis was continuing to use the same leavepiece and the same claim 'No other LMWH has more indications ….'. Therefore, Leo stated that Aventis accepted that the piece and the associated claims were in breach of the Code but had failed to correct this breach and had been unable to control the activities of its representatives.

The Panel considered that the inclusion of the licensed indication 'Treatment of VTE presenting as DVT, PE or both' and the tick for Clexane and cross for tinzaparin gave the overall impression that Clexane had an additional distinct indication of clinical relevance compared to Innohep and that was not so. A patient presenting with venous thromboembolic disease could only be treated with Clexane if the disease presented as deep vein thrombosis, pulmonary embolism or both; the same disease presentations for which Innohep was licensed. The table was misleading in this regard; a breach of the Code was ruled.

Leo Pharmaceuticals complained about a four page leavepiece (ref CLE0210301) for Clexane (enoxaparin) issued by Aventis Pharma Ltd. Pages 2 and 3 of the leavepiece were headed 'The only LMWH [low molecular weight heparin] licensed for the prevention and treatment of VTED in surgical and acutely ill medical patients'. Below this appeared a chart comparing the licensed indication for Clexane with dalteparin, tinzaparin (Leo's product, Innohep), certoparin and reviparin. The column headed 'Clexane' had ticks for all the licensed indications listed. The chart indicated that whilst Leo's product Innohep (tinzaparin) was licensed for both the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) it was not licensed for the 'Treatment of VTE [venous thromboembolic disease] presenting as DVT, PE or both'.

COMPLAINT

Leo alleged breaches of Clauses 7.2 and 7.3 of the Code. It also alleged that Aventis was failing to control the activities of its representatives and was in breach of Clause 15.10 of the Code.

Leo had written to Aventis in August 2001 and complained that it was misleading to suggest that a patient presenting with a DVT and a PE could not be treated with Innohep under the current marketing authorization and that the implication that Clexane had additional benefit over Innohep for VTED treatment was not true. Aventis had agreed that all future Clexane pieces would not use this misleading comparison.

In February 2002 the leavepiece was used at a hospital by an Aventis representative. Leo again contacted Aventis having taken the view that an elapsed period of six months was sufficient for the withdrawal of the offending material and claim.

Leo was assured that the leavepiece had been withdrawn. Leo subsequently received a letter from Aventis confirming this and a copy of an email used by Aventis to inform representatives that they should return the offending items for destruction and pointing out that the leavepiece was in breach of the Code

Leo stated that on 15 and 16 April Aventis was continuing to use the same leavepiece and the same claim 'No other LMWH has more indications ….'.

In summary therefore, Leo stated that Aventis accepted that the piece and the associated claims were in breach of the Code but had failed to correct this breach and had been unable to control the activities of its representatives.

RESPONSE

Aventis regretted that the mistaken use of a voluntarily withdrawn material (an exhibition panel) had caused a complaint to the Authority. Aventis' original agreement to withdraw the disputed promotional materials was an act of goodwill and not an admission of breach of the Code. This action was undertaken as Aventis strove to maintain the highest standards of promotional activity.

Aventis also stressed that the failure of this one representative to adhere to the voluntary withdrawal of this piece was an unfortunate occurrence, not a widespread failure of sales force management as alleged by Leo. The Aventis sales force was extensively trained on the Code to ensure that the representatives conducted themselves in a responsible, ethical and professional manner.

However, Aventis continued to dispute that the comparison was misleading, as it accurately reflected

the wording contained in the Innohep summary of product characteristics (SPC). It did not suggest that a patient presenting with DVT or a PE could not be treated with Innohep, as both these licensed indications were clearly listed with a 'tick'. Neither was there any implication that Clexane had additional benefit over Innohep for VTED treatment. The table merely pointed out a difference in the wording of the licensed indications for Clexane and Innohep (and other low molecular weight heparins). It should be noted that as the Fragmin SPC contained the wording 'Treatment of VTE presenting as DVT, PE or both', this product received a 'tick' in the table. This could hardly be described as 'unbalanced'.

Aventis stated that as a continued sign of its commitment to resolving this dispute amicably Aventis had taken the following actions; all copies of the exhibition panel (CLE0260301) and detail aid (CLE0330401) containing the phrase 'Treatment of VTE presenting as DVT, PE or both' had been removed from circulation and destroyed. Aventis had also reinforced to the sales force the importance of ensuring that all outdated material (whether voluntarily or compulsorily withdrawn) was destroyed to avoid accidental use.

PANEL RULING

The Panel noted that the Clexane SPC stated that it was indicated for, *inter alia*, 'The treatment of venous thromboembolic disease presenting with deep vein thrombosis, pulmonary embolism or both'. The Panel noted that the Innohep 20,000 IU/ml SPC stated that it was indicated for the 'treatment of deep vein thrombosis and of pulmonary embolus'; there was no mention of VTED as such. The Panel noted that there was a difference in the wording of the two SPCs, but considered that a patient presenting with venous thromboembolic disease could only be treated with Clexane if the disease presented as deep vein thrombosis, pulmonary embolism or both; the same disease presentations for which Innohep was licensed.

The Panel noted that the leavepiece at issue, beneath the subheading 'Treatment of VTED', listed treatment of DVT, treatment of PE and treatment of VTE presenting as DVT, PE or both as three separate indications. The Panel did not accept that the table merely pointed out a difference in the wording of the licensed indications for Clexane and Innohep as submitted by Aventis. The Panel considered that the inclusion of the licensed indication 'Treatment of VTE presenting as DVT, PE or both' and the tick for Clexane and cross for tinzaparin gave the overall impression that Clexane had an additional distinct indication of clinical relevance compared to Innohep and that was not so. The table was misleading in this regard; breaches of Clauses 7.2 and 7.3 were ruled.

* * * * *

Leo had also alleged a breach of Clause 15.10 of the Code which stated that companies were responsible for the activities of their representatives if these were within the scope of their employment even if they were acting contrary to the instructions which they had been given. Clause 15.10 was simply a statement of fact; it was not possible to breach that clause. In the circumstances the Director decided that there was no *prima facie* case to answer in that regard.

Complaint received **29 April 2002**

Case completed **17 June 2002**

ASTRAZENECA/DIRECTOR v NOVARTIS

Femara press release

AstraZeneca complained about a press release issued by Novartis headed 'First Direct Comparison of Two Aromatase Inhibitors Shows Femara (letrozole) is More Effective Than Anastrozole in Inhibiting Oestrogen Production in Advanced Breast Cancer', which detailed the results of a recently published paper by Geisler *et al* (2002). A breach of the undertaking given by Novartis in Case AUTH/1194/6/01 was alleged. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board. AstraZeneca marketed Arimidex (anastrozole).

AstraZeneca noted that in Case AUTH/1194/6/01 the claim 'More potent than anastrozole at suppressing oestrogen in advanced breast cancer patients', which was in a Femara leavepiece, was based on results reported in an abstract by Geisler *et al*. The Panel considered that the context in which the claim was made implied that owing to its superior potency, letrozole was clinically more effective than anastrozole. However in the absence of conclusive data this impression was incorrect and therefore misleading. A breach of the Code was ruled which was subsequently accepted by Novartis.

AstraZeneca alleged that the title of the press release gave an impression that the results of the study carried important clinical implications for patients with advanced breast cancer which as concluded in Case AUTH/1194/6/01 was inaccurate and misleading.

AstraZeneca considered that the paragraph 'Although the clinical relevance of this finding in terms of anti-tumour efficacy is yet to be determined, it should be recognised that the anti-tumour efficacy of all aromatase inhibitors relies on the suppression of oestrogen production. The results of this study show that Femara reduces oestrogen production more completely than anastrozole' invited the reader to directly associate the potency of a medicine with a clinical benefit in advanced breast cancer which was unsubstantiated and therefore misleading. Continuing to convey a message already ruled in breach in Case AUTH/1194/6/01 represented a breach of undertaking.

The Panel noted that Case AUTH/1194/6/01 had involved the claim 'More potent than anastrozole at suppressing oestrogen in advanced breast cancer patients' on a page headed 'Femara – clear advantages in early and advanced breast cancer'. Immediately beneath the heading were claims for Femara versus tamoxifen based on the results of a clinical trial. The claim for superior potency had come from the study by Geisler *et al*; the authors had not extrapolated their results to the clinical situation. The Panel had considered that within the context of which it appeared the claim implied that Femara was more clinically effective than anastrozole which was misleading. A breach of the Code was ruled.

Turning to the case now before it, Case AUTH/1309/4/02, the Panel noted that the context in which the claim appeared was different. 'First Direct Comparison of Two Aromatase Inhibitors Shows Femara (letrozole) is More Effective than Anastrozole in Inhibiting Oestrogen Production in Advanced Breast Cancer' appeared as the title to the press release; it did not appear amongst claims which otherwise referred to the clinical efficacy of Femara. The press release had only been sent to the medical press and the second paragraph opened with 'Although the clinical relevance of this finding in terms of anti-tumour efficacy is yet to be determined …'. The Panel considered that the manner in which the Geisler *et al* data had been presented and the context in which it appeared meant that the press release was sufficiently different from the mailing in Case AUTH/1194/6/01 for it not to be covered by the undertaking and assurance given in that case. The Panel thus ruled no breach of the Code.

AstraZeneca UK Limited complained about a press release issued by Novartis Pharmaceuticals UK Ltd alleging that it represented a breach of the undertaking given by Novartis in Case AUTH/1194/6/01. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance given previously by the Appeal Board.

The press release was headed 'First Direct Comparison of Two Aromatase Inhibitors Shows Femara (letrozole) is More Effective Than Anastrozole in Inhibiting Oestrogen Production in Advanced Breast Cancer' and detailed the results of a recently published paper by Geisler *et al* (2002). AstraZeneca marketed Arimidex (anastrozole).

COMPLAINT

AstraZeneca noted that in Case AUTH/1194/6/01 the claim 'More potent than anastrozole at suppressing oestrogen in advanced breast cancer patients' was ruled in breach of the Code. The claim, which was in a Femara leavepiece, was based on results reported in an abstract by Geisler *et al*. The Panel considered that the context in which the claim was made implied that owing to its superior potency, letrozole was clinically more effective than anastrozole. However in the absence of conclusive data this impression was incorrect and therefore misleading. A breach of Clause 7.2 was ruled which was subsequently accepted by Novartis.

On 1 February 2002, Novartis issued the press release in question which was based on the now published results of Geisler *et al* which had recently appeared in full in the Journal of Clinical Oncology.

AstraZeneca believed that the title of the press release gave an impression that the results of the study carried important clinical implications for patients with advanced breast cancer. This was based on

letrozole demonstrating a greater inhibition of oestrogen production over anastrozole. Yet, as concluded in Case AUTH/1194/6/01 such an impression, in the absence of head-to-head comparative studies with well recognised clinical outcomes such as time to progression and objective response, was inaccurate and misleading.

AstraZeneca added that this misleading impression was further conveyed in the body of the press release as the second paragraph read, 'Although the clinical relevance of this finding in terms of anti-tumour efficacy is yet to be determined, it should be recognised that the anti-tumour efficacy of all aromatase inhibitors relies on the suppression of oestrogen production. The results of this study show that Femara reduces oestrogen production more completely than anastrozole'.

Despite Novartis stating that the clinical relevance of oestrogen suppression had yet to be investigated, AstraZeneca considered that the above paragraph invited the reader to directly associate the potency of a medicine with a clinical benefit in advanced breast cancer patients. AstraZeneca was concerned that Novartis was deliberately attempting to deliver a message that, as a consequence of letrozole's superior oestrogen suppression, its effects on tumour proliferation in advanced breast cancer was likely to be greater than that of anastrozole. This message was unsubstantiated and therefore misleading. Continuing to convey a message already ruled in breach in Case AUTH/1194/6/01 represented a breach of undertaking in relation to that case.

Additionally, it was unclear as to whom the press release was aimed. If read by the lay or consumer press the impression that Femara was more clinically effective than anastrozole was, in AstraZeneca's opinion, more likely to be translated in subsequent press articles compared with the medical press, who might be in a better position to interpret the significance of the results.

In summary, AstraZeneca considered the Femara press release to be misleading for similar reasons as stated in Case AUTH/1194/6/01; it represented a breach of undertaking made in relation to that case in breach of Clause 22 of the Code.

The Authority asked Novartis to consider the requirements of Clauses 2 and 9.1 in addition to Clause 22.

RESPONSE

Novartis stated that in compliance with the Panel's ruling in Case AUTH/1194/6/01, all offending materials were removed immediately from circulation. Novartis noted that the Panel considered that the difference in oestrogen suppression between letrozole and anastrozole was relevant, although it could not be extrapolated to infer a difference in clinical efficacy. AstraZeneca did not appeal against the Panel's ruling on this element of the case. It was to this relative suppression of oestrogen that the press release now in question related.

Novartis stated that it issued the press release on 1 February 2002 to the medical press announcing and commenting on the publication of direct comparative oestrogen suppression data for Femara and anastrozole. This data was seen as extremely important by a majority of physicians and associated specialists involved in the field of endocrine treatment of breast cancer. Novartis stressed that the press release was not released to the lay or consumer press and was not therefore subject to the misinterpretation suggested by AstraZeneca.

The title of the press release was a simple description of the study outcome and contained no claim regarding clinical benefit. The second paragraph was a quote from one of the authors who was also one of the most pre-eminent researchers in endocrine treatment for breast cancer in the UK and had worked with all relevant compounds in this field of medicine including both Novartis and AstraZeneca.

Novartis acknowledged that it was responsible for any such quotes used in a promotional context and had therefore examined the statement carefully before agreeing to use it. The quote clearly stated that any clinical relevance of the findings was to be determined, and this fact had been given prominence by its inclusion so early in the press release.

At no point in the press release had there been any inference that greater oestrogen suppression might be better for either tumour growth inhibition or indeed overall outcome. The company was currently participating in research to establish this very question.

In summary, the press release was an accurate summary of a recently published work, which was consistent with the conclusions of the authors whilst at the same time complying with the undertaking made by Novartis in relation to Case AUTH/1194/6/01.

PANEL RULING

Case AUTH/1194/6/01 had involved a Femara mailing sent to medical and clinical oncologists in which the claim 'More potent than anastrozole at suppressing oestrogen in advanced breast cancer patients' had appeared half way down a page headed 'Femara – clear advantages in early and advanced breast cancer'. Immediately beneath the heading were claims for Femara versus tamoxifen based on the results of a clinical trial. The claim for superior potency had come from the study by Geisler *et al*; the authors had not extrapolated their results to the clinical situation. The Panel had noted that it was assumed that promotional material related to the clinical situation unless it was clearly stated otherwise. The Panel had considered that within the context of which it appeared the claim implied that Femara was more clinically effective than anastrozole which was misleading. A breach of Clause 7.2 of the Code was ruled.

Turning to the case now before it, Case AUTH/1309/4/02, the Panel noted that the context in which the claim appeared was different. 'First Direct Comparison of Two Aromatase Inhibitors Shows Femara (letrozole) is More Effective than Anastrozole in Inhibiting Oestrogen Production in Advanced

Breast Cancer' appeared as the title to a press release which detailed the results of Geisler *et al*. It did not appear amongst claims which otherwise referred to the clinical efficacy of Femara. The press release had only been sent to the medical press and the second paragraph opened with 'Although the clinical relevance of this finding in terms of anti-tumour efficacy is yet to be determined …'. The Panel considered that the manner in which the Geisler *et al* data had been presented and the context in which it appeared meant that the press release was sufficiently different from the mailing in Case AUTH/1194/6/01 for it not to be covered by the undertaking and assurance given in that case. The Panel thus ruled no breach of Clause 22. The Panel also ruled no breach of Clauses 9.1 and 2.

Complaint received **29 April 2002**

Case completed **19 June 2002**

CASE AUTH/1310/4/02

YAMANOUCHI PHARMA/DIRECTOR v PFIZER

Breach of undertaking

Yamanouchi Pharma alleged that Pfizer had breached its undertaking given in a previous case by continuing to use a Cardura XL leavepiece which had been ruled in breach of the Code. Yamanouchi had been advised that the leavepiece was last used in November 2001, however two of its representatives had found copies of it on Pfizer stands at two meetings in April 2002. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

The Panel noted that there had been an error and copies of the leavepiece which should have been withdrawn had been sent by Pfizer to certain representatives in March 2002. As a consequence the company had failed to comply with its undertaking. High standards had not been maintained, breaches of the Code, as acknowledged by Pfizer, were ruled.

The Panel noted that there was no copy of a written instruction from the product manager to marketing services regarding the destruction of the leavepiece and the submission that this might have been destroyed or the instruction might not have been issued. The Panel noted that the company had made efforts to comply with the undertaking but that these had not been wholly adequate. The Panel considered that the circumstances were such that they brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 of the Code was ruled. The Panel ruled no breach of the Code with regard to the representatives' use of the leavepiece as they had been provided with copies of it from head office.

Yamanouchi Pharma Ltd complained about the recent use of a Cardura XL leavepiece (ref 58022) by representatives of Pfizer Limited. The leavepiece had been ruled in breach of the Code. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with an undertaking. This accorded with advice previously given by the Code of Practice Appeal Board.

COMPLAINT

The Cardura XL leavepiece had been ruled in breach of Clauses 7.2 and 7.3 of the Code in Case AUTH/1217/8/01. Yamanouchi alleged that Pfizer had evidently failed to abide by its undertaking to cease use of the item forthwith, in breach of Clause 22 of the Code.

Yamanouchi had been advised that the leavepiece was last used on 1 November 2001. However, two of its representatives found copies of the leavepiece on the Pfizer stands at two meetings in April 2002. Details of the meetings in Leeds and Newmarket were provided.

Yamanouchi stated that breaches of undertaking were a very serious matter which brought the industry into disrepute. This was particularly so where there were two reported incidents in different areas. Yamanouchi therefore alleged a breach of Clause 2.

The Authority asked Pfizer to also respond in relation to Clauses 9.1 and 15.2.

RESPONSE

Pfizer was extremely disturbed to discover that a complaint had arisen concerning an alleged breach of undertaking. An allegation of this nature was taken very seriously by the company which had engaged in an extensive internal investigation.

Use of the withdrawn leavepiece was not intentional and the representatives in question were unaware that the leavepieces in their possession were the original withdrawn items from November 2001.

Pfizer stated that it gave an undertaking to the Authority on 1 November 2001 regarding Case AUTH/1217/8/01. On 1 November the Cardura XL team emailed the salesforce about the need to withdraw certain Cardura XL promotional materials relating to benign prostatic hyperplasia (BPH). The message was titled 'Urgent Information – Please Action Immediately'. The email informed the salesforce of the outcome of the Yamanouchi

complaint and gave detailed information of the actions required. The Marketing Services Department, which managed and co-ordinated storage and distribution of all Pfizer promotional materials to be used by the salesforce, was informed at this time and the relevant materials (including the leavepiece in question) were removed from OASIS (the system used by representatives to order stock), thus ensuring that representatives could no longer order the item. The product manager informed marketing services that the warehouse stock of this item should be destroyed.

Regrettably, as there was no record of this instruction Pfizer could not confirm that it was either given or received. It might be that a paper record of this correspondence was destroyed or lost during transfer of Pfizer from Sandwich to Walton Oaks during December 2001. Large quantities of paper filing were systematically destroyed in the interests of space during this time. Whatever the reason for the lack of this record, whether indeed this instruction to marketing services was ever issued and whether marketing services passed the instruction to Pfizer's warehouse (these services were provided for them by a contractor) the undeniable outcome was that the leavepiece was not destroyed at that time.

Following notification of this new complaint, Case AUTH/1310/4/02, the two hospital representatives in question were interviewed in person. Their district sales managers were also interviewed either in person or by telephone.

In November 2001 the Newmarket representative was told by the marketing department to withdraw and destroy Cardura XL BPH materials (including the leavepiece in question). She had rarely used any of these materials and destroyed the pieces she had in her possession. She next received BPH materials on 11 March. The materials received in March included BPH sales aids and a 'pack of leavepieces'. The representative accepted the delivery on the reasonable assumption that it was approved material. She attended a meeting in April. The stand contained both Viagra and Cardura XL materials. She did not remember giving out leavepieces at that meeting but believed that the leavepieces on display were the ones delivered on 11 March.

The Leeds representative remembered the withdrawal of the Cardura XL materials last November. As with the Newmarket representative he was first informed via email of the original complaint regarding the Cardura XL leavepiece, by the marketing team in head office. This message was further reinforced by separate messages from his district sales manager and his sales operations manager detailing the urgency of the matter. The representative destroyed all the items in question and made the point that he had no wish to continue using the data. In April, he set up a stand at a hospital meeting. He did not distribute materials at this meeting but was not present for the whole day owing to other commitments. He left an assortment of Viagra materials and some Cardura XL materials on display. The representative remembered receiving a delivery of Cardura XL materials earlier this year. He had reasonably assumed that anything delivered to him was approved and suitable for use.

Both representatives were unaware that they had distributed inappropriate/withdrawn materials. It appeared that they were generally using the leavepiece merely as a dosage card. This might explain their failure to notice the inside contents of the leavepiece. They had no reason to suspect that an error had been made. Both representatives had passed the ABPI medical representatives examination.

It had now become apparent that the leavepieces delivered to the representatives, in March 2002, were not the current and approved versions (CAR019) but the withdrawn versions (58022). It was not completely clear how this error was made. The marketing services manager recollected requests made by the Cardura XL product team that leavepiece 58022 be removed from the representatives' ordering system, OASIS, and that at the same time all stocks of this item should be destroyed. As stated above, there was no written confirmation of this.

The representatives received a stock delivery on 11 March containing a pack of Cardura XL leavepieces. These turned out to be item 58022 when they should have been item CAR019. Pfizer had subsequently discovered that warehouse stocks of Cardura XL leavepiece 58022 were only destroyed on 15 March. This was the source of the problem.

Pfizer stated that its investigation to determine any further facts about how such an error could have occurred was ongoing. It believed, however, that it occurred as a result of a telephone conversation between the Cardura XL product manager and marketing services. An arrangement was made to release the Cardura XL leavepiece in March this year as part of the routine dispatch of Cardura XL POA 1 (ie Plan of Action 1 – the first campaign of the year), the product manager was using an up-to-date list of Cardura XL materials whilst the marketing services administrator was using an out-of-date list which still included the 58022 leavepiece.

It might be relevant to the apparent confusion that this dispatch of materials was behind schedule. Unlike all other product materials, Cardura XL BPH materials were not listed on the POA 1 document prepared in time for the first POA of the year. This was because, in the aftermath of Pfizer's undertaking to comply with the ruling, the materials were still being amended and prepared when the POA 1 document was approved. Ironically, this lack of a formal listing of the Cardura XL materials might have contributed to the confusion between the product team and marketing services.

Thus a series of errors appeared to have occurred to bring about the regrettable re-release of item 58022.

Pfizer had taken the opportunity to review the processes in place to ensure the timely and efficient withdrawal and destruction of promotional materials once an undertaking had been made. There were in fact three actions, all initiated by the product team, in response to notification from the legal department: Firstly, the product team contacted marketing services to ask for withdrawal and destruction of the relevant items. This request and confirmation of the action should have been recorded in writing. Secondly, the product team notified OASIS (the salesforce's IT based

communication system), in writing, to remove the relevant items from the list of items from which the representatives could order and thirdly, the product team wrote to all the relevant members of the salesforce, informing them that the materials in question were not to be used and that any such materials left with customers should be retrieved and destroyed.

Investigation of the events around this situation had shown that, while the product team correctly initiated actions 2 and 3, it was evident that the materials in the warehouse were not destroyed. Pfizer regretted that it could not determine how this occurred. The instruction, on paper (subsequently lost) or by word of mouth, was not received or was not passed to the warehouse staff or was not implemented by them on receipt.

On receipt of the current complaint letter, Pfizer informed its hospital representatives on 3 May that the leavepieces they received in March were not to be used. This urgent message was followed up on 8 May by a further letter explaining the nature of the problem and containing a colour photocopy of the item in question (58022).

Pfizer took these errors very seriously and was currently seeking to re-examine its withdrawal procedures for promotional materials. It planned to update the system immediately and introduce further fail-safe procedures. The examination of the systems was in the early stages but it was confident that the amended system would ensure, as far as was possible, that a problem of this nature could not arise again. Pfizer provided a draft proposal of a procedure to improve the current processes.

Pfizer reassured the Authority and Yamanouchi that the use of the withdrawn leavepieces was accidental and occurred as a result of a most unfortunate series of errors and in no way represented disrespect for the Authority's standing. Pfizer expected its entire staff to adhere to and respect the Code. An undertaking to withdraw a promotional piece was taken very seriously. Although Pfizer understood the seriousness of this breach of its undertaking, it was surprised at Yamanouchi's immediate recourse to the Authority with no attempt to resolve the situation informally, particularly as this caused a significant delay in allowing it to investigate the issue and initiate immediate remedial action.

With regard to the specific allegations of breaches of the Code Pfizer accepted the breach of Clause 22 as clearly, in spite of best intentions, materials, which it had undertaken not to re-use, were inadvertently redistributed and displayed by representatives. Pfizer offered its sincere apology for this situation.

On investigating the events Pfizer conceded that the documentation of its withdrawal and destruction procedures for promotional materials was imperfect, causing it to re-define procedures immediately. Best standards were not maintained in this instance and Pfizer therefore accepted a breach of Clause 9.1.

Pfizer believed that the conduct of its representatives throughout had been of a high ethical standard. As the offending materials were distributed to the representatives more than five months after they had been withdrawn and, as the outer pages resembled the newly developed materials, Pfizer did not believe that the representatives could be blamed for the errors. Both representatives discharged their duties in an ethical manner and believed themselves to be in compliance with the requirements of the Code. Pfizer denied a breach of Clause 15.2.

Pfizer reassured the Authority that it continued in its undertaking not to use leavepiece 58022. The brief reappearance at two local meetings in April was accidental and in no way indicated disrespect for either the Authority or Yamanouchi. Pfizer acted quickly, on receipt of this complaint, to inform departments across the company of the problem and instigated an investigation immediately. Pfizer took reasonable steps to withdraw the materials completely, in line with the undertaking given. During the course of examining procedures, it had discovered that simply complying with the steps of the undertaking was insufficient to ensure that a withdrawn piece was not used again. The risk of the piece being used in error was not removed. This was why it had introduced specific destruction steps into the new procedure.

It might be helpful in the future if the pro-forma undertaking explicitly asked for confirmation that companies would destroy offending items in addition to discontinuing their use. This was the approach employed in the new procedure. Pfizer enclosed its draft procedure for withdrawal and destruction of promotional materials. In Pfizer's opinion, activities in this matter had been open and transparent and in no way brought discredit upon, or reduced confidence in, the pharmaceutical industry. Pfizer therefore denied a breach of Clause 2.

PANEL RULING

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

Pfizer had accepted the Panel's rulings of breaches of the Code in Case AUTH/1217/8/01 and provided the requisite form of undertaking and assurance dated 1 November 2001 stating that the Cardura XL leavepiece had last been used on 1 November.

Turning to the case now before it, the Panel noted that there had been an error and copies of the leavepiece which should have been withdrawn had been sent to certain representatives in March 2002. As a consequence the company had failed to comply with its undertaking. A breach of Clause 22, as acknowledged by Pfizer, was ruled. High standards had not been maintained. A breach of Clause 9.1 of the Code, as acknowledged by Pfizer, was ruled.

There was no copy of a written instruction from the product manager to marketing services. The Panel noted the submission that this might have been destroyed or the instruction may not have been issued. The Panel noted that the company had made

efforts to comply with the undertaking but that these had not been wholly adequate. The Panel considered that the circumstances were such that they brought discredit upon and reduced confidence in the pharmaceutical industry; a breach of Clause 2 was ruled. The Panel ruled no breach of Clause 15.2 as the representatives using the leavepiece which should have been withdrawn had been provided with copies of it by head office.

Complaint received **29 April 2002**

Case completed **20 June 2002**

CASE AUTH/1312/5/02 *NO BREACH OF THE CODE*

PHARMACIST v PFIZER

Promotion of Viagra

A pharmacist complained about an advertisement for Viagra issued by Pfizer which appeared in Pulse and comprised a photograph of a couple's clasped hands. The phrase 'SPECIAL again' appeared in the top left-hand corner of the photograph; 'Viagra' appeared in the bottom right-hand corner immediately above the claim 'Speaks for itself'.

The complainant alleged that the claim 'Viagra – Speaks for itself' was unclear and ambiguous and as such, was clearly misleading. The complainant questioned the context in which the claim was made and considered whether the reader was to infer that the claim supported every aspect of the medicine's profile.

The complainant considered that the claim did not impart any information of practical value to the health professional and that it suggested a broad and an all-encompassing superiority for Viagra which remained unproven. This claim was clearly an exaggeration and was not substantiable in the context in which it was presented.

The Panel considered that the claim 'speaks for itself' would be viewed within the context of the advertisement as a whole and that it would be seen as a general claim for the efficacy of the product within the context of a consequential beneficial effect upon the couple's relationship. The Panel did not accept that the majority of readers might infer that it related to every aspect of the medicine's profile or that it suggested a broad and all-encompassing superiority. The Panel did not consider the claim misleading, unsubstantiated or exaggerated as alleged; no breach of the Code was ruled.

A pharmacist complained about an advertisement (ref VIA 105 February 2002) for Viagra (sildenafil citrate) issued by Pfizer Limited. The advertisement had appeared in the medical press such as Pulse, 6 May and comprised a photograph of a couple's clasped hands. The phrase 'SPECIAL again' appeared in the top left-hand corner of the photograph; 'Viagra' appeared in the bottom right-hand corner immediately above the claim 'Speaks for itself'.

COMPLAINT

The complainant alleged that the claim 'Viagra – Speaks for itself' was unclear and ambiguous and as such, was clearly misleading. In what context was this claim made? Was the reader to infer that the claim supported every aspect of the medicine's profile such as efficacy, safety, cost-effectiveness or did it refer to only certain specific aspects of sildenafil?

The claim did not impart any information of practical value to the health professional and suggested a broad and an all-encompassing superiority for sildenafil which remained unproven. This claim was clearly an exaggeration and was not substantiable in the context in which it was presented.

The complainant alleged that an unqualified and all-encompassing claim, such as this, could only serve to mislead the reader.

When writing to Pfizer the Authority asked it to respond in relation to Clauses 7.2, 7.4 and 7.10 of the Code.

RESPONSE

Pfizer stated that the online version of the Oxford English Dictionary defined the phrase 'speaks for itself' as 'to be significant or self-evident'. In Pfizer's view, it was beyond argument that Viagra was and had been significant since the grant of its marketing authorization in September 1998. Indeed, Viagra was even defined in the Oxford English Dictionary, as the 'proprietary name for the drug sildenafil citrate, given orally in the treatment of impotence'. Such an inclusion in the Oxford English Dictionary applied only to a select few medicinal products and could, in itself, be regarded as significant.

The application for a marketing authorization was processed rapidly by the European Medicines Evaluation Agency because Viagra was seen as an important and innovative medicine; it was the first licensed oral medicine for the treatment of erectile dysfunction (ED).

Viagra was the joint winner of the prestigious Prix Galien for scientific excellence and innovation in 2000. Professor Sir Michael Rawlins, Chair of the National Institute for Clinical Excellence presented the award to Pfizer and said: 'This drug has become a household name'. He continued, 'It is innovative, well tolerated, and provides treatment where existing therapies have been shown to be suboptimal'.

Pfizer was awarded the Queen's Award for Enterprise for innovation in the discovery and development of Viagra. The citation for the award stated that it was granted to Pfizer 'for discovering and developing sildenafil (Viagra), the first licensed oral treatment for erectile dysfunction. Prior to the drug's introduction, most treatment for erectile dysfunction involved injection, intra-urethral administration or vacuum extraction devices. The compound is a novel, potent and selective phosphodiesterase (PDE) 5 inhibitor. Sildenafil (Viagra) has been shown to provide benefit in over 70% of individuals suffering from erectile dysfunction'.

Pfizer stated that ED was a serious medical condition which could have a considerable impact on the lives of an individual and his partner, not only in terms of their sexual relationships but also their quality of life overall. ED was frequently associated with the development reactively of other illnesses such as clinical depression. Treatments such as intracavernosal injection therapy and vacuum constriction devices were available for the treatment of ED before Viagra but these treatments were perceived by many patients to have material shortcomings either in terms of efficacy or patient acceptability. Viagra therefore represented a significant step forward in the treatment of ED as it worked regardless of the underlying cause. Presentation rates for ED had increased markedly since the marketing of Viagra. The Panel had previously accepted that Viagra had had an impact on the taboo of talking about ED. In Case AUTH/1175/4/01, the Panel stated 'The fact that [ED] was more openly discussed was in part due to the impact of Viagra'. Pfizer believed that it was widely accepted within the medical community, and also among the general population, that ED was no longer the source of great shame that it once was and that this enormous step forward was due to the availability of Viagra to a significant extent.

The advertisement appeared in medical journals; full details were provided. The readers of these journals were an intelligent and sceptical audience and Pfizer did not see that they would be misled into viewing the strapline as an all-embracing claim. The advertisement included prescribing information and referred prescribers to the summary of product characteristics before prescribing the product.

Whilst the complainant clearly viewed the advertisement as in breach of the Code, Pfizer's contention was that it was not seen as misleading or all-encompassing by the vast majority of health professionals. The audience were professionals who were extremely well educated and used to seeing pharmaceutical advertising. Pfizer failed to see how this advertisement was any different from many responsible pharmaceutical advertisements which used a strapline in order to build brand association.

Pfizer did not believe that these well educated and intelligent health professionals could be misled by this strapline into changing their prescribing decisions. In Pfizer's view, the purpose of Clause 7 of the Code was to prevent pharmaceutical companies from making claims which were misleading or which misrepresented scientific data to health professionals. This advertisement did no such thing.

Viagra had received regulatory approval in 112 countries in 25mg form; 116 countries in 50mg and 97 countries in 100mg form. In addition, up until 30 September 2000, there had been 11,313 person years of observation of patients in clinical trials of Viagra. Up until the end of 2001, it was estimated that 715 million tables had been sold, an estimated 16.4 million men treated and 97 million prescriptions written (estimated).

In Case AUTH/1175/4/01, the Panel accepted that the efficacy data of most relevance to prescribers was in the 50mg and 100mg forms as these were the most regularly prescribed. The Panel found that Pfizer's claim of efficacy in up to 80% of patients was not in breach of the Code. Pfizer could provide copies of the studies on which the Panel based its findings if required.

Pfizer submitted that there had been no breach of Clause 7.2 because the points made above demonstrated that the 'Speaks for itself' strapline was accurate, balanced, fair and objective. The advertisement had been seen by a great many health professionals and only one complaint had been made. This would suggest that there was no widespread concern that the strapline was misleading.

With regard to Clause 7.4, if Pfizer applied the Oxford English Dictionary definition of the phrase 'speaks for itself' the significance of Viagra was capable of substantiation and there could be no breach of this clause.

Clause 7.10 prohibited all-embracing and exaggerated claims. The strapline was not an all-embracing claim, nor was it an exaggeration to say that Viagra had been a significant development in the treatment of ED. The Appeal Board in Searle v Boehringer Ingelheim (Case AUTH/583/7/97) found that Boehringer Ingelheim's use of the claim 'Red carpet treatment' in its advertisement for Mobic was not an exaggeration because it was supported by a reduction in gastro-intestinal side effects of one third. Pfizer believed that the data did support the fact that Viagra spoke for itself.

PANEL RULING

The Panel considered that the claim 'Speaks for itself' would be viewed within the context of the advertisement as a whole. The advertisement featured the clasped hands of a couple and the prominent phrase 'SPECIAL again'. The Panel considered that the claim at issue would be seen as a general claim for the efficacy of the product within the context of a consequential beneficial effect upon the couple's relationship. Viagra had been a significant development in the treatment of ED. The Panel did not accept, as alleged by the complainant, that the majority of readers might infer that it related to every aspect of the medicine's profile or that it suggested a broad and all-encompassing superiority. The Panel did not consider the claim misleading, unsubstantiated or exaggerated as alleged; no breach of Clauses 7.2, 7.4 and 7.10 was ruled.

Complaint received **8 May 2002**

Case completed **18 June 2002**

CASE AUTH/1313/5/02

HOSPITAL DOCTOR v LUNDBECK

Corporate advertisement

A hospital doctor complained about a Lundbeck advertisement published in the BMJ. The advertisement was headed 'Our progression in CNS' and referred to Lundbeck's research and development in CNS with its dedication and commitment leading to many advances in treatments. Amitriptyline, lofepramine and Cipramil were named. Reference was made to scope for further discovery and to progressing towards completing a brighter picture. The advertisement finished by stating 'to find out more about our focus on CNS research, visit our website …'. The address was given. Two logos appeared at the bottom of the advertisement, one with the company name and the other was a representation of a person (referred to as a swirl genie by Lundbeck).

The complainant stated that on visiting the website referred to in the advertisement and following links to CNS research, information about escitalopram was presented which the complainant believed had not yet been granted a marketing authorization.

The complainant stated that the advertisement also displayed, slightly larger than the Lundbeck logo, the logo for escitalopram (the swirl genie). In this regard the complainant referred to an advertisement in the American Journal of Psychiatry. It was difficult to avoid the conclusion that this was an advertisement for escitalopram. The complainant alleged that the purpose was to promote awareness and interest in the product and communicated no medical or scientific information, and therefore was promotion prior to the grant of the marketing authorization. It was alleged to be 'teaser' advertising as described in the supplementary information in the Code.

The Panel noted that the swirl genie had been used in the Lexapro (escitalopram) advertisement in the American Journal of Psychiatry immediately adjacent to the product name. In the Panel's view its use was such that to the reader it appeared to be a product logo; it was difficult to see that it was supposed to be a symbol of Lundbeck and Forest's partnership as submitted by Lundbeck.

The advertisement referred to 'progressing towards completing a brighter picture'. This together with the website details was such that it would encourage readers to access the website to find out more about products in development. Although the website did not immediately refer to escitalopram, this was the first product mentioned in the pipeline section. Posters presenting the results of clinical trials could be downloaded and reference was made to the launch of the product in 2002.

The Panel considered that on balance the material promoted escitalopram prior to the grant of the marketing authorization and a breach of the Code was ruled. The Panel did not consider that the advertisement was a 'teaser' and no breach of the Code was ruled in this regard. The Panel did not consider that the material was such as to bring discredit upon or reduce confidence in the pharmaceutical industry and no breach of Clause 2 was ruled.

A hospital doctor complained about an advertisement issued by Lundbeck Ltd which was published in the BMJ, 23 March 2002.

The advertisement was headed 'Our progression in CNS' and referred to Lundbeck's research and development in CNS with its dedication and commitment leading to many advances in treatments. Amitriptyline, lofepramine and Cipramil were named. Reference was made to scope for further discovery and to progressing towards completing a brighter picture. The advertisement finished by stating 'to find out more about our focus on CNS research, visit our website …'. The address was given. Two logos appeared at the bottom of the advertisement, one with the company name and the other was a representation of a person (referred to as a swirl genie by Lundbeck).

COMPLAINT

The complainant stated that the advertisement described how Lundbeck was 'progressing towards a brighter picture' through CNS research and invited readers to visit the website to find out more. On visiting this site and following links to CNS research, information about escitalopram was presented. The complainant believed that this product had not yet been granted a marketing authorization.

The complainant stated that the advertisement also displayed, slightly larger than the Lundbeck logo, the logo for escitalopram (the swirl genie). In this regard the complainant referred to an advertisement in the American Journal of Psychiatry. It was difficult to avoid the conclusion that this was an advertisement for escitalopram. Any advertisement with a prominent logo for a particular product must be an advertisement for that product, whether this was explicit or not.

The complainant alleged that the advertisement contravened Clause 3.1, in that its purpose was to promote awareness and interest in the product and communicated no medical or scientific information, and therefore was promotion prior to the grant of the marketing authorization.

It would also seem to contravene Clause 9.1 in that it was 'teaser' advertising as described in the supplementary information in the Code.

The complainant stated that the advertisement appeared to be a clear attempt to avoid the restrictions of the Code and the more the complainant saw pharmaceutical companies pushing at the boundaries of acceptable marketing practices, the less confidence he had in the industry.

When writing to Lundbeck in addition to those clauses mentioned by the complainant it was also asked to respond in relation to Clause 2 of the Code.

RESPONSE

Lundbeck stated that it was a specialist company which solely focused its research on diseases of the central nervous system (CNS) and its mission was to improve the quality of life for those suffering from psychiatric and neurological diseases. Although it had been in the UK for 30 years it was aware that health professionals were neither as aware of the company's research-based heritage nor of its missions and values as it would have expected. This was the reason, therefore, that it had been running a corporate advertisement. As a Foundation, a large part of Lundbeck's income, approximately one quarter, was reinvested into clinical research and development (R&D), hence the mention of CNS research in the advertisement.

The website was a public, corporate, site that could be accessed easily by anyone searching for 'Lundbeck'. Printed copies of the complete site were supplied. The site contained information that was available to the public not only through the Internet but also by various independent financial institutions. Whoever entered this site was not directed or linked directly to any data about escitalopram.

From the front page of the website one could enter the Research and Development page, this had eight areas indicated for further viewing: Research and Development at Lundbeck; Drug Discovery; Drug Development; R&D areas; Animal ethics; Pipeline; Our Partners; Publications. None of these areas was highlighted or given undue prominence over other sub-texts. All the areas covered within these sections contained factual, scientific, balanced information that was of both general and scientific interest.

If one then clicked on to 'Pipeline' the open page contained a list of the 10 products currently in the pipeline listed (as in all corporate data, such as financial reports) in the order of their stage of clinical development; none was given any undue prominence. One could then click on the various products to see a brief scientifically accurate, balanced, non-promotional statement.

Thus the advertisement did not direct one to escitalopram and even someone who knew the site would have to make at least a minimum of four clicks to see anything about the product. The site, anyway, was accessible to the worldwide general public and was maintained by the H Lundbeck Corporation, its headquarters in Copenhagen, Denmark. There was obviously no compulsion (through the advertisement) for health professionals either to access the Internet or to log onto any specific site. The information contained within the site on escitalopram was miniscule in comparison to the content of the whole site, but was nevertheless scientifically balanced and non-promotional.

Escitalopram had been licensed via the Mutual Recognition (MR) procedure. The first licence within the EU was granted in Sweden on 7 December 2001. Following the 90 day MR process approval, including the UK, was granted on 8 May 2002. National licences should be provided within 30 days of this approval.

Lundbeck explained that the logo that appeared on the corporate advertisement, 'a swirl genie', was developed in collaboration with its US partner Forest Laboratories. It was a symbol that could be used in all future joint ventures with Forest as a symbol of the partnership and as a 'global' acknowledgement of that partnership. Lundbeck's collaboration with Forest covered many areas of joint interest. This included the clinical development of escitalopram and of compounds for the treatment of dementias (eg Memantine) but also the marketing of citalopram in the US. Lundbeck did not have an active sales organization in the US and it had not taken out any advertisements in the US. Through this complaint it had been made aware, therefore, of the advertisement in the American Journal of Psychiatry. This was a Forest advertisement for escitalopram and appeared to have incorporated the partnership logo.

This logo, which was not specifically an escitalopram logo, had appeared on a number of other corporate communications, eg mailers, note/mouse pads. These had been distributed to both primary (GP) and secondary (psychiatrists) care since January 2002.

In conclusion Lundbeck denied that the advertisement was intended either to promote the use of any of its products, including escitalopram, prior to the granting of a marketing authorization, or to act as a 'teaser' advertisement. The company denied any breaches of Clause 3.1 and 9.1. Furthermore as an ethical pharmaceutical company with a focus of R&D in the CNS area, that reinvested one quarter of its income into this area, Lundbeck considered that informing health professionals of its heritage did not breach Clause 2.

PANEL RULING

The Panel noted that the advertisement at issue used a logo which had been used in the advertisement for Lexapro (escitalopram) in the American Journal of Psychiatry. The Panel noted that it was not necessary unacceptable *per se* to include logos on corporate advertisements. In the Panel's view the juxtaposing of the swirl genie immediately adjacent to the product name in the advertisement in the American Journal of Psychiatry was such that to the reader it appeared to be a product logo. It was difficult to see that the logo was supposed to be a symbol of Lundbeck and Forest's partnership. The American advertisement provided to the Panel did not mention Lundbeck at all. In the Panel's view the swirl genie would be seen as a product logo and had been used by Forest as such.

The Panel considered that the advertisement at issue was on the borderline of acceptability. The advertisement referred to 'progressing towards completing a brighter picture'. This together with the website details was such that it would encourage readers to access the website to find out more about products in development. It was true that the website did not immediately refer to escitalopram although this was the first product mentioned in the pipeline section. Posters presenting the results of clinical trials could be downloaded and reference was made to the launch of the product in 2002.

The use of the swirl genie logo which had clearly been associated with the advertising of escitalopram in the US was of concern.

The Panel considered that on balance the material promoted escitalopram prior to the grant of the marketing authorization and a breach of Clause 3.1 of the Code was ruled.

The Panel did not consider that the advertisement was a 'teaser' as referred to in the supplementary information to Clause 9.1 because that related to a situation where promotional material teased the recipient by eliciting an interest in something which would be following or would be available at a later date without providing any actual information about it. In the Panel's view the advertisement implied that as a result of its research and development, Lundbeck would be introducing a new CNS product. No breach of Clause 9.1 was ruled.

Clause 2 was used as a sign of particular censure and reserved for such use. The Panel did not consider that the material was such as to bring discredit upon or reduce confidence in the pharmaceutical industry and no breach of Clause 2 was ruled.

Complaint received **9 May 2002**

Case completed **10 July 2002**

CASES AUTH/1321/5/02 and AUTH/1322/5/02

HOSPITAL CHIEF PHARMACIST v PHARMACIA and PFIZER

Celebrex journal advertisement

A hospital chief pharmacist complained about a journal advertisement for Celebrex (celecoxib) issued by Pharmacia and Pfizer. The advertisement referred to the National Institute for Clinical Excellence (NICE) having reviewed the use of COX-2 selective inhibitors.

The advertisement stated 'COX-2 selective inhibitors should be used in preference to standard NSAIDs in any one of the following patient groups:'. Five categories of patient were then listed including 'Previous clinical history of upper GI ulcers, bleeds or perforations' and 'Serious co-morbidity'.

The complainant noted that the NICE guidelines stated, with reference to patients with a previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation, that 'The use of even a COX-2 selective agent should therefore be considered especially carefully in this situation'. This was clearly intended to mean that there might be some risk attached to the use of COX-2 medicines in such patients and that great care was needed. This very important message was absent and might result in patients being put at risk.

The complainant stated that as far as serious co-morbidity was concerned, a very common condition in patients being considered for NSAID therapy was cardiovascular disease. The NICE guidance (Section 1.5) made it clear that COX-2 selective NSAIDs might not be appropriate in such cases. Nowhere was this stated and the complainant alleged that the advertisement was over simplified and potentially dangerously misleading in this respect.

The Panel noted that reference was made to previous cases, Cases AUTH/1293/4/02 and AUTH/1294/4/02, which concerned a leavepiece for Celebrex which similarly referred to the NICE guidance and stated that COX-2 selective inhibitors should be used in preference to standard NSAIDs in the following groups of patients with osteoarthritis and rheumatoid arthritis, listing, *inter alia*, previous clinical history of upper GI ulcers, bleeds or perforations. The complainant had alleged that 'the leavepiece appeared to misquote the NICE guidance and noted that the guidance actually said that very careful consideration of any agent, even a COX-II selective agent, was required in patients with serious co-morbidity or previous GI bleed or perforations'.

The NICE guidance stated 'The risk of NSAID-induced complications is particularly increased in patients with a previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation. The use of even a Cox II selective agent should therefore be considered especially carefully in this situation'.

The Panel had noted the submission that by emphasising the words *'in preference to standard NSAIDs'* in the leavepiece the companies had presupposed that the clinician had made the appropriate risk/benefit assessment. The patient groups listed needed different risk/benefit assessments. Although the leavepiece correctly described one group of potentially high risk patients as those with 'Previous clinical history of upper GI ulcers, bleeds or perforations', it did not state, as did the NICE guidance, that this group was particularly vulnerable to GI complications and that the use of even COX-2 agents should be considered especially carefully in this situation. The Panel had considered that the leaflet was misleading in this regard and a breach of the Code was ruled.

The parties accepted the Panel's rulings and the case concluded a few days before the present complaint was received.

With regard to the present cases, Cases AUTH/1321/5/02 and AUTH/1322/5/02, the Panel decided that, with regard to the allegation about the use of COX-2 selective inhibitors in patients with 'Previous clinical history of upper GI ulcers, bleeds or perforations', the rulings in Cases AUTH/1293/4/02 and AUTH/1294/4/02 applied and a breach of the Code was ruled.

With regard to the allegation concerning serious co-morbidity, NICE guidance stated that in patients with cardiovascular disease there remained uncertainty over the use of COX-2 selective inhibitors and they should not therefore be prescribed routinely in preference to standard NSAIDs where these were indicated in this group of patients. Many patients with cardiovascular disease received low-dose aspirin and this carried an increased risk of GI events. In patients receiving low dose aspirin the benefit of using COX-2 selective agents (to decrease gastrointestinal toxicity) was reduced. Prescribing COX-2 selective agents preferentially over standard NSAIDs in this situation was not justified on current evidence. Section 4.10 of the NICE guidance summarised the clinical effectiveness data, concluding that there remained some concern regarding potential cardiovascular risks associated with COX-2 selective medicines and caution was needed, as it was for standard NSAID therapy, when prescribing in patients with pre-existing cardiovascular disease.

The summary of product characteristics (SPC) stated that Celebrex was contraindicated in patients with severe congestive heart failure. It referred to the need for caution in patients with a history of cardiac failure, left ventricular dysfunction or hypertension and in patients with pre-existing oedema from any other source. The prescribing information in the advertisement included similar information.

The Panel noted that the advertisement made no specific mention of prescribing Celebrex for cardiovascular disease. The reference to serious co-morbidity was a reflection of the NICE guidance in relation to using COX-2 selective inhibitors in preference to standard NSAIDs in the listed patient groups.

There was some uncertainty regarding the use of COX-2 selective inhibitors in patients with pre-existing cardiovascular disease. The position was not straightforward. Section 1.5 of the NICE guidance, which provided that in patients with cardiovascular disease COX-2 selective inhibitors should not be prescribed routinely in preference to standard NSAIDs, appeared to be inconsistent with Section 1.3 which advocated that they were recommended only in patients at high risk of developing serious GI side effects.

The Panel considered that on balance the advertisement was not unreasonable with regard to patients with serious co-morbidities. The Panel ruled no breach of the Code.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure nor did it warrant a ruling in relation to a failure to maintain high standards; no breach of those clauses was ruled.

A hospital chief pharmacist complained about a journal advertisement (ref 83867-P6905/10/01 October 2001) for Celebrex (celecoxib) issued by Pharmacia Limited and Pfizer Limited. The advertisement had appeared in a wide range of journals for health professionals including GUT, Pulse, Doctor, the BMJ and Hospital Doctor and referred to the National Institute for Clinical Excellence (NICE) having reviewed the use of COX-2 selective inhibitors.

COMPLAINT

The complainant was concerned that the advertisement misquoted the NICE guidance in such a way that might result in some patients being put at risk.

The advertisement stated 'COX-2 selective inhibitors should be used in preference to standard NSAIDs in any one of the following patient groups:'. Five categories of patient were then listed including 'Previous clinical history of upper GI ulcers, bleeds or perforations' and 'Serious co-morbidity'.

In fact the NICE guidelines explicitly stated with reference to patients with a previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation that 'The use of **even** (emphasis added by the complainant) a Cox II selective agent should therefore be considered especially carefully in this situation'. This was clearly intended to mean that there might be some risk attached to the use of COX-2 medicines in such patients and that great care was needed. This very important message was completely absent from the material and might result in patients being put at risk. The practice at the complainant's hospital was to suggest that, when these patients did require NSAID therapy, a proven gastro-protective drug regimen (normally a proton pump inhibitor (PPI) plus a standard NSAID) was the treatment choice.

The complainant stated that as far as serious co-morbidity was concerned, a very common condition in patients being considered for NSAID therapy was cardiovascular disease. The NICE guidance (Section 1.5) made it clear that COX-2 selective NSAIDs might not be appropriate in such cases. Nowhere in the advertisement was this stated and the complainant contended that the material was over simplified and potentially dangerously misleading in this respect.

When writing to Pharmacia and Pfizer, the Authority asked them to respond in relation to Clauses 2, 7.2, 7.9 and 9.1 of the Code and also noted that a similar item had been considered earlier in Cases AUTH/1293/4/02 and AUTH/1294/4/02.

RESPONSE

Separate, but similar, responses were received from Pharmacia and Pfizer.

The companies stated that as pointed out by the Authority, this complaint was almost identical to that in Cases AUTH/1293/4/02 and AUTH/1294/4/02

which concerned a leavepiece in respect of which undertakings were given on 17 May 2002.

By way of background, Pharmacia and Pfizer stated that the advertisement in question provided a summary of the NICE guidance on the use of cyclo-oxygenase II (COX-2) selective inhibitors. The first appearance was on 3 August 2001. However, following the undertakings in the earlier cases, this advertisement now at issue was withdrawn because it was considered to be of a similar nature to the material in that complaint. The prescribing information appeared alongside the advertisement. The advertisement did not give the impression that the material was quoted directly from the guidance. The Panel had accepted this point when considering the previous cases.

The remit of NICE was to appraise new technologies in terms of their clinical and cost effectiveness. It was intended that their recommendations would be implemented throughout the NHS to avoid the inequity in healthcare that had been the subject of considerable publicity in recent years.

Pharmacia and Pfizer supported the aims of NICE and wished to see patients in England and Wales having equal access to advances in the management of osteo- and rheumatoid arthritis. Reproducing the entire guidance document or a comprehensive summary of it was not possible in a journal advertisement. The companies therefore publicised the main recommendations of the guidance, in order to raise awareness of it among a wide body of prescribing health professionals. The audience that this item was aimed at was a sophisticated and sceptical one which would recognise that this was a summary of the main recommendations rather than a comprehensive summary of the whole guidance.

Reference to the guidance was included on the advertisement in question. The Panel, however, did not accept that this meant that prescribers might refer to it for further detail, when considering the earlier cases. The leavepiece previously at issue was therefore not deemed to be a stand-alone item, and the companies had accepted this point.

With respect to the complainant's first point: 'Previous history of upper GI ulcers, bleeds or perforations', the companies noted the following points.

They were surprised that some clinicians would find this misleading, and as pointed out above, it was a referenced summary of the guidance. They did, however, accept the Panel's ruling and had therefore discontinued use of this advertisement. The companies strongly disputed that this would in any way put patients 'at risk' – they were only suggesting that a COX-2 selective inhibitor be used in the situation where an NSAID would otherwise have been prescribed. Nowhere in the NICE guidance was there any suggestion that the COX-2 inhibitors were more damaging to the gastrointestinal tract than traditional NSAIDs.

It would appear that the complainant had misunderstood the guidance. In his letter he stated that 'Our own practice is to suggest that, in such patients who do require NSAID therapy, a proven gastro-protective drug regimen (normally a PPI plus a standard NSAID) is the treatment of choice'. The patient population to which he was referring should, according to NICE, be prescribed a COX-2 selective agent in preference to a standard NSAID. Section 1.3 of the guidance stated that patients 'at high' risk of developing serious gastrointestinal disease should be prescribed COX-2 selective inhibitors in preference to standard NSAIDs, and section 2.10 listed a previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastrointestinal complications as being in the high risk group. The guidance stated that this group was at especially high risk, and the use of a COX-2 selective inhibitor should be considered especially carefully in this situation.

As a result of the undertakings given in the previous cases, the current materials included full reference to the special care needed in this group as Pharmacia and Pfizer were committed to the ethical and accurate presentation of the NICE guidance.

Section 2.9 of the guidance stated that gastro-protective agents including PPIs 'have been shown to be only partially effective in the prophylaxis and treatment of NSAID related gastrointestinal events. They are not without additional side effects and add significantly to the total cost of drug therapy'. Indeed PPI's had not been shown prospectively to decrease ulcer complications (Rostom *et al* Cochrane Library Issue 3.200).

Section 1.6 of the guidance further stated that 'There is no evidence to justify the simultaneous prescription of gastro-protective agents with COX II selective inhibitors as a means of further reducing potential gastrointestinal adverse events'.

With respect to the complainant's second point concerning serious co-morbidity, the allegation was that the material was over simplified and potentially dangerously misleading. NICE itself in section 1.5 on the guidance stated that 'there remains uncertainty over the use of COX II selective inhibitors and they should not therefore be prescribed routinely in preference to standard NSAIDs where these are indicated in this group of patients'. The companies believed that this comment was based on NICE's uncertainty regarding their advantage, rather than the association with proven dangerous side effects. NICE went on to state in section 4.7 that '… the potential risk [of COX II's in cardiovascular disease] should be taken into consideration when prescribing selective COX II inhibitors in patients with cardiovascular disease, *as is the case with all NSAIDs*' (emphasis added by Pharmacia and Pfizer). This statement again referred to the uncertainty in this area. The companies also referred the Panel to the previous cases where the Panel found that the companies were not in breach of the Code for use of this statement. Despite this, however, they had amended this statement in the current materials due to the uncertainty.

In fact the concern regarding COX-2 selective inhibitors and cardiovascular disease had been clarified, subsequent to the NICE guidance, with the Committee on the Safety of Medicines (CSM) guidance. This related specifically to rofecoxib (one of

the two coxibs assessed in the NICE report). The CSM guidance had reminded prescribers that rofecoxib was contra-indicated in patients with congestive cardiac failure and caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and in patients with oedema for any other reason. The CSM guidance did not make similar recommendations for celecoxib.

The supplementary information to Clause 2 of the Code stated that a ruling of a breach of this clause was a sign of particular censure and was reserved for such circumstances. Pharmacia and Pfizer believed that the advertisement was a responsible and ethical presentation of the major points of the NICE guidance. The Panel found in the previous cases that the advertisement did not have the appearance of a direct quotation from the guidance. After the undertaking, the companies withdrew this advertisement as well as the leavepiece at issue in those particular cases.

For these reasons, Pharmacia and Pfizer submitted that this advertisement did not warrant the censure of a ruling of a breach of Clause 2.

As regards Clause 7.2, the earlier cases clearly applied. The omission of the guidance's warning that care was needed before prescribing even a COX-2 selective inhibitor to those patients with a previous history of gastrointestinal complications, was in breach of Clause 7.2.

The companies asked that the Panel found there to be no breach of Clause 7.2 in relation to patients with serious co-morbidity needing similar consideration as those with a history of gastrointestinal problems, as this was the finding on this point in the earlier cases.

In relation to Clause 7.9, the advertisement did not claim that Celebrex was safe or without side effects. In addition, the prescribing information listed the information required by the Medicines (Advertising) Regulations. The advertisement did not, in the companies' view, make claims about side effects which did not reflect the evidence. Therefore a ruling that the advertisement was in breach of this clause was not warranted.

Pharmacia and Pfizer submitted that the advertisement was a responsible and ethical attempt to publicise the guidance to health professionals. Although a similar item was found to be in breach of Clause 7.2 of the Code in the earlier cases, the style of the advertisement was not likely to cause offence so as to be in breach of Clause 9.1. The companies submitted that this clause was not intended to cover the present cases. In the event that the Panel did not accept this, the companies would submit that this was already covered by Clause 7.2.

Pharmacia and Pfizer reiterated that this advertisement was withdrawn as part of the undertakings given in Cases AUTH/1293/4/02 and AUTH/1294/4/02 and that the materials had now been changed to reflect that ruling of the Panel and to more comprehensively communicate the guidance, and to better reflect uncertainties contained within it. As this was a complaint regarding the same issues as the previous cases, the companies did not believe that any additional breaches should be ruled. In addition, breaches of Clauses 2, 7.9 and 9.1 were not supported by the facts in these cases.

PANEL RULING

The Panel noted that reference was made to previous cases; Cases AUTH/1293/4/02 and AUTH/1294/4/02 which concerned a leavepiece for Celebrex which similarly referred to the NICE guidance. The leavepiece referred to the NICE guidance and stated that COX-2 selective inhibitors should be used in preference to standard NSAIDs in the following groups of patients with osteoarthritis and rheumatoid arthritis, listing, *inter alia*, previous clinical history of upper GI ulcers, bleeds or perforations. The complainant had alleged that 'the leavepiece appeared to misquote the NICE guidance and noted that the guidance actually said that very careful consideration of any agent, even a COX-II selective agent, was required in patients with serious co-morbidity or previous GI bleed or perforations'.

Relevant extract from the Panel's ruling in Cases AUTH/1293/4/02 and AUTH/1294/4/02:

'The NICE guidance referred to in the leavepiece was entitled 'Guidance on the use of cyclo-oxygenase (Cox) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis'. Section 1.3 of the guidance stated 'Cox II selective inhibitors are not recommended for routine use in patients with rheumatoid arthritis (RA) or osteoarthritis (OA). They should be used, in preference to standard NSAIDs, when clearly indicated as part of the management of RA or OA only in patients who may be at 'high risk' of developing serious gastrointestinal adverse effects'.

Section 1.4 of the NICE guidance described high risk patients. The first half of the paragraph identified such patients as those aged 65 years or over, those taking concomitant medicines known to increase the likelihood of upper GI adverse events, those with a serious co-morbidity or those requiring prolonged use of maximum recommended doses of standard NSAIDs. The second half of the paragraph read 'The risk of NSAID-induced complications is particularly increased in patients with a previous clinical history of gastroduodenal ulcer, gastrointestinal bleeding or gastroduodenal perforation. The use of even a Cox II selective agent should therefore be considered especially carefully in this situation'.

Beneath the introductory statement 'COX-2 selective inhibitors should be used *in preference to standard NSAIDs* in the following group of patients with OA and RA' was boxed text stating 'Patients aged 65 years or over'. The leavepiece continued by stating 'or in any of the following patient groups': 'Prolonged use of standard NSAIDs at their maximum recommended doses', 'Previous clinical history of upper GI ulcers, bleeds or perforations', 'Co-prescribed with mediations known to increase the likelihood of upper GI adverse events' and 'Serious co-morbidity'.

The Panel noted the submission that by emphasising the words *'in preference to standard NSAIDs'* the

companies had presupposed that the clinician had made the appropriate risk/benefit assessment. The patient groups noted needed different risk/benefit assessments. Although the second bullet point in the box of text correctly described one group of potentially high risk patients as those with 'Previous clinical history of upper GI ulcers, bleeds or perforations', it did not state, as did the NICE guidance (Section 1.4), that this group was particularly vulnerable to GI complications and that the use of even COX-2 agents should be considered especially carefully in this situation. It appeared from the leaflet that NICE considered patients in this particularly high risk group to be no more vulnerable than other high risk patients such as those aged 65 years or above which was not so. The Panel considered that the leaflet was misleading in this regard; a breach of Clause 7.2 was ruled.

The Panel noted that the complainant stated that the patient group with serious co-morbidity needed similar especially careful consideration before considering prescribing a COX-II selective agent according to the NICE guidance; this was not so. No breach of Clause 7.2 of the Code was ruled in this regard.'

The parties accepted the Panel's rulings and the case concluded on 17 May. The present complaint was received on 20 May.

Cases AUTH/1321/5/02 and AUTH/1322/5/02

Paragraph 5.1 of the Constitution and Procedure provided, *inter alia*, 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 was not the subject of appeal to the Code of Practice Appeal Board. The Director thus decided that the present complaint in relation to the category of patient described as having 'Previous clinical history of upper GI ulcers, bleeds or perforations' was closely similar to that decided previously in Cases AUTH/1293/4/02 and AUTH/1294/4/02 which were not the subject of an appeal. The allegation regarding serious co-morbidity was different to that previously considered. The Director decided that the present case should thus proceed.

The Panel decided that, with regard to the allegation about the use of COX-2 selective inhibitors in patients with 'Previous clinical history of upper GI ulcers, bleeds or perforations', the rulings in Cases AUTH/1293/4/02 and AUTH/1294/4/02 applied and a breach of Clause 7.2 was ruled as acknowledged by the companies.

With regard to the allegation concerning serious co-morbidity the Panel noted that Section 1.5 of the NICE guidance stated that in patients with cardiovascular disease there remained uncertainty over the use of COX-2 selective inhibitors and they should not therefore be prescribed routinely in preference to standard NSAIDs where these were indicated in this group of patients. Many patients with cardiovascular disease received low-dose aspirin and this carried an increased risk of GI events. In patients receiving low dose aspirin the benefit of using COX-2 selective agents (to decrease gastrointestinal toxicity) was reduced. Prescribing COX-2 selective agents preferentially over standard NSAIDs in this situation was not justified on current evidence. Section 4.10 of the NICE guidance summarised the clinical effectiveness data concluding that there remained some concern regarding potential cardiovascular risks associated with COX-2 selective medicines and caution was needed, as it was for standard NSAID therapy, when prescribing in patients with pre-existing cardiovascular disease.

Section 4.3 of the summary of product characteristics (SPC) stated that Celebrex was contraindicated in patients with severe congestive heart failure. Section 4.4 of the SPC referred to the need for caution in patients with a history of cardiac failure, left ventricular dysfunction or hypertension and in patients with pre-existing oedema from any other source. The prescribing information in the advertisement included similar information.

The Panel noted that the advertisement made no specific mention of prescribing Celebrex for cardiovascular disease. The reference to serious co-morbidity was a reflection of the NICE guidance in relation to using COX-2 selective inhibitors in preference to standard NSAIDs in the listed patient groups.

The Panel queried the relevance of the submission that the CSM guidance that rofecoxib was contra-indicated in patients with congestive cardiac failure and that caution should be exercised in patients with a history of cardiac failure, left ventricular dysfunction or hypertension and in patients with pre-existing oedema or for any other reason and that similar recommendations had not been made for Celebrex. The Panel accepted that similar recommendations had not been made by the CSM for Celebrex but the CSM statement for rofecoxib appeared to reflect the Celebrex SPC.

There was some uncertainty regarding the use of COX-2 selective inhibitors in patients with pre-existing cardiovascular disease. The position was not straightforward. Section 1.5 of the NICE guidance which provided that in patients with cardiovascular disease COX-2 selective inhibitors should not be prescribed routinely in preference to standard NSAIDs appeared to be inconsistent with Section 1.3 which advocated that they were recommended only in patients at high risk of developing serious GI side effects.

The Panel considered that on balance the advertisement was not unreasonable with regard to patients with serious co-morbidities. The Panel ruled no breach of Clauses 7.2 and 7.9 of the Code.

The Panel did not consider that the circumstances either warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure nor did it warrant a ruling of a breach of Clause 9.1 in relation to a failure to maintain high standards; no breach of those clauses were ruled.

Complaint received **20 May 2002**

Case completed **8 July 2002**

CASE AUTH/1326/5/02

CONSULTANT PHYSICIAN v PROCTER & GAMBLE

Didronel PMO advertisement

A consultant physician complained about a Didronel PMO (etidronate disodium/calcium carbonate) journal advertisement issued by Procter & Gamble. The advertisement was headed 'Didronel PMO – A common sense fracture defence' and compared Didronel PMO with alendronate (Merck Sharp & Dohme's product Fosamax). A claim 'Comparable increase in BMD [bone mineral density] at the spine and hip – Didronel PMO and alendronate 10mg' was referenced to Sahota *et al* (2000). A bar chart (beneath the claim) headed 'Spine BMD increase over 1 year' compared the percentage change in BMD vs baseline for Didronel PMO and alendronate 10mg. There was a small visual difference in favour of alendronate 10mg. It was stated that there was no significant difference between the treatments.

The complainant was distressed to see the advertisement claiming that the study by Sahota *et al* showed that there was no significant difference between Didronel PMO and alendronate. While it might be accepted that there was not a significant difference with respect to BMD changes between the two medicines, the study was not powered to evaluate this, thus these claims could not be made. The claim did not reflect the conclusions of the referenced study. A breach of the Code was alleged.

The Panel noted that Sahota *et al* was a 12 month, open label, randomized, controlled, prospective treatment study in 140 postmenopausal women with established vertebral osteoporosis which compared the gain in BMD, reduction in bone turnover markers and adverse event profile of continuous alendronate, cyclical alendronate and cyclical etidronate with calcitriol.

The discussion part of the study stated 'There was a trend towards greater gain in BMD in the continuous alendronate group followed by the cyclical etidronate and cyclical alendronate groups, although these changes were not significantly different; however it must be recognised that the study was not powered to examine this effect'. The study authors concluded that limitations in the study design were recognized, 'in particular with respect to statistical power to show differences between the bisphosphonate groups, but more importantly fracture endpoints'.

The Panel noted that the claim at issue and data presented directly compared Didronel PMO and alendronate 10mg. The claim was asterisked to a statement beneath the bar chart which read 'published prospective, randomized study of Didronel PMO and alendronate 10mg in the treatment of post-menopausal osteoporosis'. The advertisement implied that Sahota *et al* was powered to directly compare Didronel PMO and alendronate with respect to gains in BMD and that was not so as acknowledged by the study authors. The asterisk reinforced the implied direct comparison. The Panel considered that the comparison was misleading and was not capable of substantiation; breaches of the Code were ruled.

A consultant physician complained about a Didronel PMO (etidronate disodium/calcium carbonate) journal advertisement (ref EBUD002) issued by Procter & Gamble Pharmaceuticals UK Limited. The advertisement had appeared in many publications including BMJ, 25 May.

The advertisement was headed 'Didronel PMO – A common sense fracture defence' and compared Didronel PMO with alendronate (Merck Sharp & Dohme's product Fosamax). A claim 'Comparable increase in BMD [bone mineral density] at the spine and hip – Didronel PMO and alendronate 10mg' was referenced to Sahota *et al* (2000). A bar chart (beneath the claim) headed 'Spine BMD increase over 1 year' compared the percentage change in BMD vs baseline for Didronel PMO and alendronate 10mg. There was a small visual difference in favour of alendronate 10mg. It was stated that there was no significant difference between the treatments.

COMPLAINT

The complainant was distressed to see the advertisement claiming that published data showed that there was no significant difference between Didronel PMO and alendronate which was referenced to a study.

The complainant stated that while it might be accepted that there was not a significant difference with respect to bone mineral density changes between the two medicines, the study was not powered to evaluate this, thus these claims could not be made. The claim did not reflect the conclusions of the referenced study. A breach of the Code was alleged.

The Authority asked Procter & Gamble to respond in relation to Clauses 7.2, 7.3 and 7.4 of the Code.

REPONSE

Procter & Gamble stated that it was no longer using the claim in question and a new advertisement had been commissioned.

Procter & Gamble's reasons for making this claim was firstly that the statements were factually correct, the graph provided the data taken directly from the study, and the graph was clearly labelled. Secondly, despite the study not being powered to assess between-group effects, the authors themselves discussed differences between the bisphosphonate arms of the study, and presented data side by side. Statistical testing of between-group effects was carried out for cyclical etidronate and cyclical alendronate and reported as not significant. The abstract stated 'We report a 12 month, open labelled, randomized controlled, prospective treatment study … comparing the effect of continuous alendronate, cyclical alendronate and cyclical etidronate with calcitriol in terms of increasing BMD' and 'cyclical alendronate appears to be effective in comparison with continuous treatment'. This was based on a non-significant between-group difference of 1.6% at the spine and 1%

at the hip. Comparing cyclical etidronate and continuous alendronate (ie the licensed regimens), these differences were much smaller: only 0.8% and 0.4% respectively. Procter & Gamble believed that using the same criteria, the authors must also believe that cyclical etidronate also appeared to be effective in comparison with continuous alendronate.

However, recent evidence suggested that increase in BMD with anti-resorptive medicines only accounted for a small part of the observed fracture risk reduction. Given this new evidence, Procter & Gamble considered it was important not to overplay the importance of a surrogate marker of fracture efficacy when fracture data were available. Procter & Gamble no longer included BMD data in Didronel PMO advertising and focussed instead on the clinically meaningful endpoint of fracture.

Nonetheless Procter & Gamble acknowledged the comments made by the complainant, and apologised for any distress caused by the advertisement.

PANEL RULING

The Panel noted that Sahota *et al* was a 12 month, open label, randomized, controlled, prospective treatment study in 140 postmenopausal women with established vertebral osteoporosis which compared the gain in BMD, reduction in bone turnover markers and adverse event profile of continuous alendronate, cyclical alendronate and cyclical etidronate with calcitriol. Both the cyclical and continuous alendronate groups and the Didronel PMO group showed significantly greater gains in BMD compared with the calcitriol group at both the anteroposterior spine and total hip.

The discussion part of the study stated 'There was a trend towards greater gain in BMD in the continuous alendronate group followed by the cyclical etidronate and cyclical alendronate groups, although these changes were not significantly different; however it must be recognised that the study was not powered to examine this effect'. The study authors concluded that limitations in the study design were recognized, 'in particular with respect to statistical power to show differences between the bisphosphonate groups, but more importantly fracture endpoints'. The authors further concluded that the study provided evidence that continuous alendronate and cyclical etidronate were effective in a comparable treatment population and were more effective than calcitriol in terms of gain in BMD and reduction in bone turnover. Reference was made to the need for further studies with fracture endpoints.

The Panel noted that the claim at issue and data presented directly compared Didronel PMO and alendronate 10mg. The claim was asterisked to a statement beneath the bar chart which read 'published prospective, randomized study of Didronel PMO and alendronate 10mg in the treatment of post-menopausal osteoporosis'. The advertisement implied that Sahota *et al* was powered to directly compare Didronel PMO and alendronate with respect to gains in BMD and that was not so as acknowledged by the study authors. The asterisk reinforced the implied direct comparison. The Panel considered that the comparison was misleading and was not capable of substantiation; breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

Complaint received **28 May 2002**

Case completed **8 July 2002**

CODE OF PRACTICE REVIEW – AUGUST 2002

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1234/10/01	**Schwarz Pharma v Schering-Plough**	**NeoClarityn mailing**	**Breaches Clauses 7.2, 7.3 and 7.4** **Audit of Schering-Plough's procedures to check implementation of previous audit recommendations as required by Appeal Board** **Public Reprimand by ABPI Board**	**Appeal by respondent** **Report from Appeal Board to ABPI Board**	**Page 3**
1241/10/01	**Chiron Corporation v Forest Laboratories**	**Promotion of Colomycin**	**Breaches Clauses 3.2 and 7.2**	**Appeal by complainant**	**Page 8**
1259/11/01	**Pharmacia v Allergan**	**Promotion of Lumigan**	**Breaches Clauses 7.2 and 7.8**	**Appeal by complainant**	**Page 14**
1262/12/01	**Bristol-Myers Squibb and Sanofi-Synthelabo v Merck Sharp & Dohme**	**Promotion of Cozaar**	**Four breaches Clause 3.2**	**Appeal by complainants**	**Page 21**
1266/12/01	**Health Authority v Abbott Laboratories**	**Obesity symposium**	**Breaches Clauses 2, 9.1 and 19.1**	**Appeal by complainant**	**Page 30**
1272/1/02	**Pharmacia v GlaxoSmithKline Consumer Healthcare**	**Promotion of NiQuitin CQ lozenge**	**Three breaches Clause 7.2** **Breaches Clauses 7.3 and 7.4**	**No appeal**	**Page 34**
1273/2/02	**Primary Care Group Pharmaceutical Adviser v Aventis Pharma**	**Telfast mailing**	**Breach Clause 7.2**	**No appeal**	**Page 40**
1274/2/02	**Merck Sharp & Dohme v Pfizer**	**Promotion of Lipitor**	**Two breaches Clause 3.2** **Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 42**
1275/2/02	**Voluntary admission by AstraZeneca**	**Breach of undertaking**	**Breaches Clauses 2 and 22**	**No appeal**	**Page 47**
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1278/2/02	**Primary Care Group Pharmaceutical Adviser v Trinity**	**Conduct of representative**	**Breach Clause 9.1**	**No appeal**	**Page 55**
1279/2/02	Health Authority Medical Adviser v GlaxoSmithKline	Conduct of representative	No breach	No appeal	Page 58

1280/2/02	**Novo Nordisk v Solvay Healthcare**	**Femoston-conti leavepiece**	**Breach Clause 7.2**	**Appeal by respondent**	**Page 61**
1282/2/02	**NHS Trust Audit Pharmacist v Wyeth**	**Prescribing guidance**	**Breach Clause 9.1**	**No appeal**	**Page 65**
1283/2/02	**Dermal Laboratories v Crookes Healthcare**	**Promotion of Unguentum M**	**Breaches Clauses 7.2, 7.4 and 7.10**	**No appeal**	**Page 67**
1284/3/02 & 1306/4/02	**Merck Sharp & Dohme v Bristol-Myers Squibb and Sankyo Pharma**	**Promotion of Lipostat**	**Breaches Clauses 7.2, 7.3 and 7.10**	**No appeal**	**Page 69**
1285/3/02	**Media/Director v Pfizer**	**Lipitor journal advertisement**	**Breaches Clause 7.2, 7.4 and 7.10**	**No appeal**	**Page 71**
1286/3/02	**General Practitioner v Aventis Pharma**	**Omission of non-proprietary name**	**Breach Clause 4.3**	**No appeal**	**Page 73**
1287/3/02	**Merck Sharp & Dohme v Procter & Gamble**	**Didronel PMO mailing**	**Two breaches Clause 7.2 Two breaches Clause 7.3 Breaches Clauses 7.8, 7.9 & 8.1**	**No appeal**	**Page 74**
1289/3/02	**Medical Director of an Ambulance Service NHS Trust v Roche**	**Promotion of Rapilysin**	**Breach Clause 9.1**	**No appeal**	**Page 77**
1291/3/02	**Pfizer v Lilly**	**Promotion of tadalafil at an international meeting**	**Breach Clause 3.1**	**No appeal**	**Page 81**
1292/3/02	**AstraZeneca v Trinity**	**Promotion of Pulvinal inhalers**	**Eleven breaches Clause 7.2 Breach Clause 7.3 Three breaches Clause 7.4 Breach Clause 7.10**	**No appeal**	**Page 84**
1293/4/02 & 1294/4/02	**Health Authority Assistant Director, Medicines and Prescribing v Pharmacia and Pfizer**	**Celebrex leaflet**	**Breach Clause 7.2**	**No appeal**	**Page 97**
1295/4/02	General Practitioner v Crookes Healthcare	Provision of camera	No breach	No appeal	Page 100
1296/4/02	**Consultant Psychiatrist v Pfizer**	**Advertisement to the public**	**Breach Clause 20.2**	**No appeal**	**Page 104**
1297/4/02	**Schering-Plough v Aventis Pharma**	**Promotion of Telfast**	**Three breaches Clause 7.2 Three breaches Clause 7.3**	**No appeal**	**Page 107**
1301/4/02	**Pfizer v GlaxoSmithKline**	**Report in The Sun**	**Breach Clause 20.2**	**No appeal**	**Page 110**
1302/4/02	General Practitioner v Novartis	Advertisement to the public	No breach	No appeal	Page 113
1307/4/02	**Primary Care Trust Pharmaceutical Advisor v Roche Products**	**Promotion of MabThera**	**Two breaches Clause 7.2**	**No appeal**	**Page 115**

1308/4/02	**Leo v Aventis Pharma**	**Clexane leavepiece**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 117**
1309/4/02	AstraZeneca/Director v Novartis	Femara press release	No breach	No appeal	Page 119
1310/4/02	**Yamanouchi Pharma/Director v Pfizer**	**Breach of undertaking**	**Breaches Clauses 2, 9.1 and 22**	**No appeal**	**Page 121**
1312/5/02	Pharmacist v Pfizer	Promotion of Viagra	No breach	No appeal	Page 124
1313/5/02	**Hospital Doctor v Lundbeck**	**Corporate advertisement**	**Breach Clause 3.1**	**No appeal**	**Page 126**
1321/5/02 & 1322/5/02	**Hospital Chief Pharmacist v Pharmacia and Pfizer**	**Celebrex journal advertisement**	**Breach Clause 7.2**	**No appeal**	**Page 128**
1326/5/02	**Consultant Physician v Procter & Gamble**	**Didronel PMO advertisement**	**Breaches Clauses 7.2, 7.3 and 7.4**	**No appeal**	**Page 133**

PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about seventy non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Nicholas Browne QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).