

CODE OF PRACTICE REVIEW

PMCPA

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 ABPI Code of Practice for the Pharmaceutical Industry independently of the Association itself.

COMPLAINTS IN 2008 DOWN ON 2007

In 2008 the PMCPA received 112 complaints as compared with 127 in 2007. There were 134 complaints in 2006, 101 in 2005, 119 in 2004, and 131 in 2003.

The average number of complaints received each year since the PMCPA was established at the beginning of 1993 is 123, the numbers in individual years ranging from 92 in 1993 to 145 in both 1994 and 1997.

There were 104 cases to be considered in 2008, as compared with 122 in 2007. The number of cases usually differs from the number of complaints because some complaints involve more than one company and others do not become cases at all, usually because they do not show that there may have been a breach of the Code.

The number of complaints from health professionals in 2008 (44) exceeded the number from pharmaceutical companies (both members and non-members of the ABPI) (33). Complaints made by pharmaceutical companies are generally more complex than those from outside the industry, usually raising a number of issues.

Six complaints were made by members of the public and five by pharmaceutical company employees, three of these by anonymous employees. There were fifteen other anonymous complaints and three complaints were made by organisations.

The remaining six complaints were nominally made by the Director and arose from media criticism, voluntary admissions by companies and alleged breaches of undertakings.

PAPERS FOR APPEAL

When preparing an appeal against a decision of the Code of Practice Panel or responding to an appeal care should be taken as to the nature and quantity of material to be submitted as evidence.

Brevity may not always be possible when complex matters are appealed but a clear and concise exposition of the facts should be aimed at. Repetition of the same point should be avoided. All points should be covered in the main text without the use of footnotes.

When a published paper etc is referred to, it must be provided and it assists the Appeal Board if an indication is given as to what members are expected to glean from it and whereabouts in it they should look.

There have recently been appeals where a number of unnecessary documents were provided, mainly references to which the party concerned did not refer at all in its letter. There is little or no merit in merely submitting a large number of published papers without any commentary on them.

The Appeal Board asked that companies be reminded to follow the Guidance on Appeal Procedures as published on the PMCPA website (www.pmcpa.org.uk).

ROYAL COLLEGE OF PHYSICIANS REPORT

A Royal College of Physicians Working Party, chaired by Dr Richard Horton, has published a report 'Innovating for Health-Patients, physicians, the pharmaceutical industry and the NHS'. The PMCPA submitted evidence to the Working Party as did the ABPI. The PMCPA will be looking carefully at the recommendations particularly those that refer to the PMCPA.

BYE NIAMH

Niamh MacMahon, who has been with the Authority since 2006 as Communications Manager, has recently moved to Novartis Pharmaceuticals UK Ltd to become its Senior Corporate Communications Manager. The Authority thanks Niamh for all her hard work on its behalf and wishes her success in her new role.

CODE OF PRACTICE TRAINING

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

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

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

Monday, 23 March

Monday, 27 April

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 Nora Alexander for details (020 7747 1443 or email nalexander@pmcpa.org.uk).

HOW TO CONTACT THE AUTHORITY

Our address is:

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

www.pmcpa.org.uk

Telephone: 020 7747 8880
Facsimile: 020 7747 8881

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

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

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

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

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

PHARMACIST PRACTITIONER v SANOFI-AVENTIS

Provision of promotional aids for Acomplia

A pharmacist practitioner complained that no response had been received when he had returned reply paid cards for Acomplia (rimonabant) sent to him by Sanofi-Aventis.

The complainant stated that the practice recently received several reply paid cards for Acomplia announcing that the National Institute for Health and Clinical Excellence (NICE) had recommended this medicine for obesity.

The card offered copies of four rimonabant clinical studies and also some other items that the practice would have found useful (a laptop case, a USB stick and a laser pointer). The complainant indicated on the card that he did not want to see a representative. Four weeks had passed since the complainant completed and returned the card and the requested items had not been delivered.

The detailed response from Sanofi-Aventis is given below.

The Panel noted Sanofi-Aventis' arrangements for dealing with responses (via reply paid cards) to its mailings. It noted that Sanofi-Aventis had not received the complainant's reply paid card and that the company now assumed that it had got lost in the post. In the circumstances the Panel did not consider that the failure to deliver the requested items to the complainant meant that high standards had not been maintained. No breach of the Code was ruled, which was upheld by the Appeal Board on appeal by the complainant.

A pharmacist practitioner complained that he had received no response when he had returned reply paid cards for Acomplia (rimonabant) sent to him by Sanofi-Aventis.

COMPLAINT

The complainant stated that the practice recently received several reply paid cards for Acomplia announcing that the National Institute for Health and Clinical Excellence (NICE) had recommended this medicine for obesity.

The card offered copies of four rimonabant clinical studies and also some other items that the practice would have found useful (a laptop case, a USB stick and a laser pointer). The complainant indicated on the card that he did not want to see a representative. Four weeks had passed since the complainant completed and returned the card and the requested items had not been delivered. The complainant had not been informed by any of the

reception staff that anyone had called to see him from Sanofi-Aventis and in this respect they were very reliable; the complainant had had items delivered by or seen representatives from other companies in this time.

When writing to Sanofi-Aventis, the Authority asked it to respond in relation to Clause 9.1 of the Code.

RESPONSE

Sanofi-Aventis stated that it always aimed to maintain high standards in all matters.

Sanofi-Aventis submitted that it had only sent one reply paid card describing Acomplia NICE guidance since the guidance was announced on 25 June 2008. Although the complaint referred to the practice receiving several cards Sanofi-Aventis had assumed that this referred to more than one copy of the mailing in question as no other cards had been sent out.

Use of the reply paid card commenced on 7 July and mailers were sent on a named basis to doctors at the complainant's practice, with a general mailer to 'the pharmacist' on 10 July, by second class post. It was anticipated that these mailers would have arrived at the practice on 14 July. The only record of a card being returned from the practice was dated 15 July and was from a GP, not the complainant. Sanofi-Aventis had no record of a card being returned by the complainant.

Sanofi-Aventis explained that its reply paid cards were sent out by an agency. Each card was coded with a territory number designated by the area to which it was posted. Cards, returned by second class post from the health professional to the agency, were forwarded to the relevant representative. The contract with the agency did not specify a timeframe for this; however it used a weekly dispatch to send the cards to the representatives. When the representatives received the cards, they ordered the materials requested from the company's warehouse on a monthly basis. The materials were then sent to the representative to be delivered to the health professional in question. In this particular instance, the reply paid card from the doctor at the complainant's practice was sent to the appropriate representative on 1 August. This representative would then order items from the warehouse, most likely in their August order, to be delivered to the doctor in the future. There was normally eight to twelve weeks between the health professional returning the reply paid card and him receiving the items requested.

If the health professional indicated that they did not wish to see a representative, the items would be left with the receptionist at the surgery. This was standard policy endorsed by Sanofi-Aventis and the reply paid card made it clear that there was no obligation to see a representative. In addition, all representatives were fully trained and briefed regarding the Code, and in particular, Clause 15.3 relating to not employing inducement or subterfuge to gain an interview and the relevance of this to reply paid cards.

It was not possible to be more specific about the interval between the card being returned and dispatch of the items as this varied. Sanofi-Aventis noted that reply paid cards were sent by second class post and thus treated as low priority by the postal services. This alone could result in significant delays in requests arriving. Additionally, if cards missed either the weekly mail from the agency to the representative, or the monthly order from the representative, delays were inevitable. Beyond this cards might be lost in the post, an event wholly out of the company's control.

From the company's investigation it appeared that the earliest the complainant could have returned the reply paid card was around 14 July. The complaint was received by the Authority on 6 August, a timeframe of less than four weeks. As stated above, however, Sanofi-Aventis did not appear to have received a card from the complainant and it could only assume that it might have been lost in the post.

Sanofi-Aventis added that, to date, it had not received any other complaints about this reply paid card or delivery of items. In addition, Sanofi-Aventis had not had any previous complaints regarding the other reply paid cards. Sanofi-Aventis believed that its processes were reasonable and robust and that a delay of eight to twelve weeks from posting date to receipt of promotional items was not unreasonable given the nature of such items.

In view of the level of quantity and quality of service generally provided to date in these matters and the absence of previous complaints, Sanofi-Aventis believed that this demonstrated that it had maintained high standards and was therefore not in breach of Clause 9.1.

PANEL RULING

The Panel noted Sanofi-Aventis' arrangements for dealing with responses (via reply paid cards) to its mailings. It noted that Sanofi-Aventis had not received the complainant's reply paid card and that the company now assumed that it had got lost in the post. In the circumstances the Panel did not consider that the failure to deliver the requested items to the complainant meant that high standards had not been maintained. No breach of Clause 9.1 was ruled.

APPEAL BY COMPLAINANT

The complainant alleged that it was most convenient that this complaint had been diverted into a failure of the mail delivery services rather than of Sanofi-Aventis, especially as the complainant had returned such cards in the past and yielded no response. In addition, the Royal Mail admitted that, by its own estimates, 99.93% of mail was delivered. In all probability, based on this statistic, the complainant considered that his reply paid card was indeed delivered. The complainant wondered what systems were in place to record delivery of these cards that could be produced to demonstrate failed delivery.

The complainant was further disappointed that in light of such blameless conduct Sanofi-Aventis had, as yet, failed to instruct its local representative to deliver the clinical papers as originally requested or attempted some other means of delivery.

The complainant thought that as Sanofi-Aventis had been accused of failing to respond to a simple reply paid card, it would try to resolve the situation to the satisfaction of the complainant. The complainant considered that perhaps in the future he should return several cards from different post boxes in order to minimise the likelihood of the post being lost.

COMMENTS FROM SANOFI-AVENTIS

Sanofi-Aventis submitted that in response to the complaint it had already outlined how this process operated, but summarised the key points. The original mailer, including the reply paid card, was sent to a list of general practitioners and the pharmacist, with the name and address pre-stamped on the reply paid card. No reply paid card was received by the agency containing the complainant's name or from the pharmacist at this practice. However, a reply paid card was received from one of the named general practitioners at the practice. This particular reply paid card had been forwarded to the local representative to trigger the ordering of the items requested for subsequent delivery to the named GP, according to their instructions.

Although Sanofi-Aventis could understand the complainant's frustration, it had to rely on external agencies for this process to be completed. It was in the company's interest to ensure that items such as clinical papers were provided to clinicians upon request, and Sanofi-Aventis also regretted that in this instance the fulfilment of the request had not been possible. This appeared to be outside the control of the company, as indicated in the original response, and Sanofi-Aventis was not able to make any further submission other than to outline again the facts that had occurred, as above.

Sanofi-Aventis noted that the complainant was disappointed that Sanofi-Aventis had not acted

upon this complaint and sought to deliver the items to him. Sanofi-Aventis would have been more than happy to do this had the complainant contacted the company direct but a complaint to a third party did not represent a *bona fide* request to the company. In the absence of such a direct request there was no desire to respond in what might be considered an unsolicited manner, given that such an action might be considered in breach of the Code. Should the complainant desire a copy of the clinical papers mentioned in the initial complaint, a simple request to the medical information department would be all that was necessary.

FINAL COMMENTS FROM COMPLAINANT

The complainant noted that his complaint was in respect of Sanofi-Aventis' failure to respond to a reply paid card requesting clinical papers for rimonabant (Acomplia). The card was completed and returned on 9 July and requested that four clinical papers were delivered to the practice along with other items, including a laptop case, that the complainant thought the practice might find useful.

In response to the complaint Sanofi-Aventis had stated that no card was received from the complainant although it confirmed that cards were sent to each of the named doctors and one to 'the pharmacist'. This latter card was the one returned by the complainant.

The complainant noted Sanofi-Aventis' reliance on external agencies and that it regretted that it had failed to fulfil his request in this instance. The complainant was unsure exactly what the term external agencies implied but he had already noted the small amount of mail that was lost annually by Royal Mail. If Sanofi-Aventis was referring to companies that were subcontracted to manage these cards, perhaps a more robust system of management was required.

In addition, the complainant suggested that if Sanofi-Aventis had a genuine reason to regret its failure to fulfil his request then surely it would have instructed its local representative to call on him having been given his details as part of this complaint. Sanofi-Aventis advised that any such contact might be considered an unsolicited approach.

There were several points here that were worthy of further discussion. Firstly, Sanofi-Aventis appeared to be unsure if such an approach would constitute a breach of the Code given that the phrase might be considered as unsolicited was hardly conclusive. Additionally, the fact that the complainant had complained about failure to respond to a card returned via the post surely indicated that his request was not unsolicited. The very fact that he had stated that he had returned a card meant his request was solicited and this was further reinforced by the fact that he had complained about

a failure to respond to his request.

Setting this aside, the complainant noted out that almost all visits from company representatives were unsolicited. A representative could have been dispatched to see him with instructions to apologise for not having responded earlier, explain that no card had been received and offer to correct this if he still desired it. The complainant did not believe that this could have been construed as a breach of the Code.

If this approach had not been appropriate then Sanofi-Aventis could have posted items. Clause 10 of the Code applied to provision of reprints. It stated that these could not be provided unsolicited unless they had been refereed. The supplementary information to Clause 10.1 of the Code stated that, when providing an unsolicited reprint of an article about a medicine, it should be accompanied by prescribing information. Since the main request was for clinical papers (which had been peer reviewed before publication in a journal and therefore refereed before this publication) this implied that the papers could have been mailed directly provided that prescribing information such as a summary of product characteristics was included in the mailing.

In summary, the complainant sympathised that Sanofi-Aventis might not have received his card, however he alleged that this was highly unlikely and he still could not understand the apparent lack of interest in rectifying this situation if indeed Sanofi-Aventis genuinely regretted its failure to fulfil his request. There had been ample time and opportunity to satisfy his original request but this opportunity had not been taken. Events over the last few days had meant that a request to the medical information department for the papers was now moot because the medicine had been withdrawn following recommendations from the European Medicines Evaluation Agency.

APPEAL BOARD RULING

The Appeal Board noted Sanofi-Aventis' arrangements for dealing with responses (via reply paid cards) to its mailings. It noted Sanofi-Aventis' submission that it had not received the complainant's reply paid card and that the company had assumed that it had got lost in the post. This was disputed by the complainant. However in these circumstances the Appeal Board did not consider that the failure to deliver the requested items to the complainant prior to the submission of the complaint meant that high standards had not been maintained. The Appeal Board upheld the Panel's ruling of no breach of Clause 9.1. The appeal was unsuccessful.

Complaint received **6 August 2008**

Case completed **13 November 2008**

ANONYMOUS EMPLOYEE v ROCHE

Cystic fibrosis patient adherence and incentive programme

The complainant wrote as an anonymous employee of Roche who was very concerned over the lack of action with reference to an adherence programme that the company had run since 2004 and that continued today.

The complainant understood that the programme incentivised children and teenagers suffering from cystic fibrosis (CF) to stay on Pulmozyme treatment. The concept was one that the complainant realised was needed and he/she understood it was not outwith the Code but the complainant did not know whether this was an acceptable means to sell a product.

The complainant was concerned that the incentive was a payment of a £10 voucher or gift card for certain high street stores. Effectively Roche was paying children to continue with a prescription only medicine and the NHS was paying for the medicine which was clearly financially more significant than £10.

The scheme was that a doctor would prescribe Pulmozyme which was presented in an ampoule with a removable cap. The patient would collect the caps and for every 30 returned to Roche's agency the patient would be sent a £10 voucher for the shop of their choice. Every 30 ampoules used meant £10 to the child or parent to spend.

There was no guarantee that the children actually took the medicine as prescribed; they could just take the tops off and get the money. The complainant was particularly concerned that if they had a side effect and either still remained on treatment or just wasted the NHS money by fulfilling the next prescription without taking the medicines, then this raised concerns over patient safety.

The complainant also knew that paying patients to take a medicine was potentially against the law and as such the complainant wished to remain anonymous but had no option but to present the details as set out above.

The detailed response from Roche is given below.

The Panel noted that no new patients had been enrolled since September 2007 and the patient adherence and incentive programme had been finally stopped in September 2008. The letter to patients notifying them of changes and the closure of the programme was dated June 2007. The case was considered under the 2006 Code using the 2008 Constitution and Procedure.

The Panel noted Roche's submission that daily

adherence with Pulmozyme was particularly important in CF and that Pulmozyme was the only medicine in its class.

The Panel accepted that there were difficulties with adherence but did not consider the incentive scheme run by Roche was an appropriate means of encouraging patients to take their medicine. There was nothing about the scheme which ensured that patients took Pulmozyme as prescribed. The adherence programme booklet for patients included a section clearly labelled 'The Incentive'. The section labelled 'Your questions answered' mentioned the importance of taking Pulmozyme every day, whether there were symptoms or not. This was in line with the product's summary of product characteristics (SPC).

The Panel noted that Roche representatives were given cycle goals (2004 and 2005) of recruiting patients to the adherence programme. Representatives were, according to Roche, initially financially rewarded on the number of patients enrolled. It was assumed that this would be by means of promoting the scheme to health professionals who would complete the enrolment form. The Panel was concerned that the scheme might have influenced the prescribing of Pulmozyme.

Roche submitted that it had instructed the agency to stop the incentive scheme by the end of September 2007. However this had not happened and vouchers continued to be sent out until the end of May 2008. This showed a serious lack of control by Roche.

The Panel was extremely concerned about the arrangements for many reasons. However it did not consider that the incentive scheme amounted to a gift, benefit in kind or pecuniary advantage given or offered to health professionals or administrative staff as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. The benefit, in the form of vouchers for high street stores, was to patients not individual health professionals. The Panel thus ruled no breach of the Code.

The Panel did not consider that the vouchers were promotional aids as such. They were clearly linked to the use of the medicine. The vouchers were not promotional aids for health professionals and thus there could be no breach of the Code.

The Panel considered that gifts to patients was a difficult area. There was little guidance in the Code and little case precedent. However the Panel was

very concerned about a pharmaceutical company in effect providing cash as an incentive to patients to use its medicine.

The Panel considered that once enrolled into the programme, and knowing about the £10 vouchers, patients would be likely to ask their doctor to prescribe Pulmozyme and thus a breach of the Code was ruled.

The Panel considered that the incentive scheme was totally unacceptable. It did not consider that Roche had maintained high standards. A breach of the Code was ruled. The Panel considered that the arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel also considered that the incentive scheme for patients warranted consideration by the Appeal Board in relation to the possibility of additional sanctions. In addition the Panel was concerned that Roche's procedures had allowed vouchers to be distributed for over 6 months after the scheme had closed. The company was currently suspended from membership of the ABPI in relation to another matter. The Panel decided to report Roche to the Appeal Board in accordance with Paragraph 8.2 of the 2008 Constitution and Procedure.

Roche accepted all the Panel's rulings of breaches of the Code.

The Appeal Board accepted that daily treatment with Pulmozyme was particularly important in CF. Irrespective of whether or not the scheme complied with the Code, the Appeal Board was concerned that a patient adherence scheme was introduced with no means of measuring its effectiveness. The scheme was aimed at patients aged between eight and sixteen. The choice of the high street stores seemed odd given this age group.

The Appeal Board was extremely concerned that vouchers were still being distributed following Roche's decision to withdraw the programme in September 2007 and instructions to its agency at this time. This showed a serious lack of control by the company.

The Appeal Board noted that Roche was currently suspended from membership of the ABPI and undergoing a series of audits (Cases AUTH/2099/2/08 and AUTH/2100/2/08 and AUTH1819/4/06). The Appeal Board was very concerned about Case AUTH/2165/9/08 but decided that in the circumstances no further action was required in relation to possible further sanctions.

An anonymous employee complained about Roche Products Limited's cystic fibrosis (CF) patient adherence and incentive programme. Roche marketed Pulmozyme (dornase alpha) for the management of CF.

COMPLAINT

The complainant stated that having recently received a large amount of ABPI training, awareness of what was right and wrong had been raised and as such the complainant wrote as a member of Roche who was very concerned over the lack of action with reference to an adherence programme that the company had run since 2004 and that continued today.

The complainant understood that the programme incentivised children and teenagers suffering from CF to stay on Pulmozyme treatment. The concept was one that the complainant realised was needed and he/she understood it was not outwith the Code but the complainant did not know whether this was an acceptable means to sell a product.

However, the complainant's concern was that the incentive was a payment of a £10 voucher or gift card for Boots, Tesco and Toys R Us. Effectively Roche was paying children to continue with a prescription only medicine and the NHS was paying for the medicine which was clearly financially more significant than £10.

The system was that a doctor would prescribe Pulmozyme and the patient got the medicine. Pulmozyme was presented in an ampoule with a removable cap. The patient would collect the caps and for every 30 returned to the agency acting on Roche's behalf the patient would be sent a £10 voucher for the shop of their choice. Every 30 ampoules used meant £10 to the child or parent to spend.

There was no guarantee that the children actually took the medicine as prescribed by their doctor and they could just take the tops off and get the money. The complainant was particularly concerned that if they had a side effect and either still remained on treatment or just wasted the NHS money by fulfilling the next prescription without taking the medicines, then this raised concerns over patient safety.

The complainant knew that this was potentially a very serious matter but with the company being suspended and the fact that senior management had known about this for over three months but not closed it down, as the complainant felt they should have, they were now acting irresponsibly and did not take action because of profit over safety.

The complainant also knew that paying patients to take a medicine was potentially against the law and as such the complainant wished to remain anonymous but had no option but to present the details as set out above so the authorities could investigate further and make their own judgement.

When writing to Roche, the Authority asked it to respond in relation to Clauses 2, 9.1, 18.1 and 22.2 of the Code and to consider the supplementary information to Clause 18.2 about items given to or

for use by patients. Except for the numbering of Clause 22.2 (formerly Clause 20.2) these were all the same in the 2006 Code as in the 2008 Code.

RESPONSE

Roche stated that it had considered very carefully whether its historical actions in relation to the CF patient adherence and incentive programme could fairly be said to constitute breaches of Clauses 2, 9.1, 18.1 and 22.2 of the 2008 Code.

Background summary

In 2004, in discussions with clinicians who treated CF, Roche was made aware of the particular problem of patient compliance. Roche then devised health educational materials concerning CF intended to encourage children and teenagers to take Pulmozyme every day as prescribed. Pulmozyme was supplied in ampoules for use with a nebuliser.

In 2007, it was decided to replace the voucher system for the adherence and incentive programme with an on-line educational programme as a way of encouraging more effective adherence. All patients who were enrolled in the programme at that time were sent letters informing them that the voucher scheme was to close in September 2007. Since then, no new patients had been enrolled in the voucher programme.

Although the agency running the programme on Roche's behalf was instructed by Roche to send letters out to patients in order to end the programme, in June 2008 Roche discovered that applications for vouchers were still being processed.

Chronological order of events

- June 2004 Adherence programme developed
- August 2004 Adherence programme certified
- September 2004 CF adherence programme live
- By September 2007 Voucher scheme closed and moved to on-line education. Roche told agency to advise patients and health professionals of closure by letter
- June 2008 Discovery of vouchers still being reimbursed
- June – August 2008 Investigation period
- July 2008 All health professionals contacted with written declaration of closure
- August 2008 Patient letters produced to reinforce closure
- September 2008 Letters sent to patients who had claimed since 2007

Cystic fibrosis

CF was the UK's most common, life-threatening, inherited disease with over 8,000 people affected. One of the symptoms of CF was thick mucus production resulting in frequent lung infections. Often, symptoms of CF appeared in infancy and childhood.

One of the treatments for CF was Pulmozyme, a recombinant human deoxyribonuclease, which broke down DNA in the sputum, thus decreasing its viscosity. Pulmozyme was the only medicine in its class and there was no therapeutic alternative to it that worked in the same way. Pulmozyme, combined with other treatments, helped prevent chronic inflammation and infection and consequent damage to the lungs.

Regular use of Pulmozyme prevented the decline in lung function that ultimately resulted in the need for lung transplantation or contributed to patient death. Compliance was particularly important because every day of treatment missed was another day that a child's lungs were exposed to the damaging effects of mucus. Furthermore, clinical trials had shown that the beneficial effects of Pulmozyme were lost if a patient only used Pulmozyme intermittently and were not regained if the patient later restarted regular therapy. This made daily adherence a vital feature of Pulmozyme therapy (Pulmozyme summary of product characteristics (SPC) Section 4.2).

With the advent of modern treatments, the proportion of CF patients becoming adults had increased as had the median life expectancy and many patients now lived into their 40s compared to 1990 for example, when girls had a median survival age of 25, 30 years for males (US CF registry data).

Adherence programme detail

In 2004, Roche UK began an adherence and incentive programme. The programme was developed following discussions with clinicians and a child psychologist regarding the problems of patient compliance with CF, and was intended to encourage children and teenagers to take their medicine as prescribed (once daily). Patients were advised of the programme by their doctor, who would complete an enrolment form and send it to an external agency which managed the programme on behalf of Roche. The agency provided the patients with an introduction booklet that contained educational material on CF including background information on CF, tips to help increase compliance, including daily adherence record sheets, and questions and answers concerning CF generally. The last page of this booklet contained a voucher request form which could be completed and returned to the agency. In exchange for 30 Pulmozyme ampoule tops, the agency would provide a voucher or gift card for £10 together with a new claim form and free post envelope for the next set of ampoule tops. Roche was informed of

the names of doctors enrolling patients, the number of patients enrolled, and how many vouchers had been requested. Doctors received no payment or other benefit for enrolling patients. The agency informed clinicians which of their patients had taken up the programme.

The programme went through Roche's internal approval procedure but the company had not retained all documents surrounding the process. The programme was explained by sales representatives to treating clinicians. Representatives were initially financially rewarded on the number of patients enrolled.

By October 2005 at an advisory board meeting, UK key doctors were informed that the programme included: 302 registered patients, 185 patients had returned tops, 34 CF centres had registered, average of 8.8 patients per centre, average adherence rate – 44% and average adherence rate of responders – 64%.

In April 2006, Roche changed the external agency involved with the programme. At that time there were 367 patients enrolled and 69 consultants participating.

Closure of the CF adherence programme

By July 2007, numbers in the programme had increased to 501 patients and 71 consultants. At that time, it was decided to replace the programme with a web based educational tool. The agency wrote to the patients then in the programme to let them know of this change and to explain that any outstanding claims for vouchers should be submitted by 20 September 2007. It seemed that this did not have the effect of ending the original programme entirely and the agency continued to receive tops and send out vouchers until the end of May 2008. All of these claims were submitted by patients enrolled before September 2007 as no new patients had been enrolled since that date. Since the end of September 2007, 160 patient claims had been received and 254 vouchers had been sent. As of 15 September 2008 there were claims from 10 patients seeking a total of 31 vouchers.

The fact that the programme had not ended from September 2007 came to light when a brand manager left Roche and files were examined. It then became apparent that vouchers were still being sent out by the agency despite it being thought that the programme had been closed.

Roche action

Roche had investigated the facts surrounding the programme. All health professionals involved in treating CF patients were telephoned to ensure that it was clear that the programme had ended. Roche contacted the 70 CF clinicians at the end of July 2008 to confirm that the programme was closed and to provide a declaration that they had no registration forms in their possession. In addition,

all those patients who had claimed since September 2007 received a certified letter, sent by recorded delivery by the agency, to again reinforce the closure of the programme.

Breach of Code – Clauses 2, 9.1, 18.1, 22.2

The Authority asked Roche to consider the complaint in the light of the 2008 Code. The one significant difference which the Authority might consider relevant to the investigation of this complaint was that, whilst the 2008 and 2006 Codes required express certification of non-promotional activities, the 2003 Code did not. In fact, the CF adherence programme was vetted for compliance with the Code in 2004 when it was introduced but Roche drew this point to the Authority's attention should it later become relevant to its determination. In that event, Roche would rely on the provisions of the 2003 and 2006 Codes in judging actions taken during the currency of those Codes.

Roche did not consider that it was possible to claim that the CF adherence programme amounted to a breach of Clause 18.1 of the 2008 (or 2003 or 2006) Code. Clause 18.1 was written in the same terms in each of the Codes and reflected the provisions of Directive 2001/83/EC and the transposing Medicines (Advertising) Regulations 1994. The aim, as set out in Recital 50 to the Directive and as clearly drafted in the Directive, Regulations and Code was that:

'Persons qualified to prescribe medicinal products must be able to carry out those functions objectively without being influenced by direct or indirect financial inducements.'

Clause 18.1 of the Code provided that:

'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine, subject to the provisions of Clause 18.2.'

At no time during the operation of the CF adherence programme was any gift, benefit in kind or pecuniary advantage offered or given to any health professional or to any administrative staff, whether as an inducement to prescribe, administer, recommend, buy or sell any medicine or otherwise. The CF adherence programme did not amount to the distribution of a promotional aid, consequently, the final proviso relating to Clause 18.2 was not relevant.

With regard to the supplementary information to Clause 18.2 'Gifts To or for Use by Patients', Roche submitted that since the CF adherence programme was not a promotional programme and did not involve the distribution of promotional aids, Clause 18.2 was not relevant. The concept of an adherence programme that would be attractive to children with CF when set against the discomfort and disruption of daily nebulisers was clearly highly relevant to

their treatment and as Roche had explained, arose originally out of advice it had received from CF consultants. Roche acknowledged the intention behind the clear words of the supplementary information to Clause 18.2 preventing the offer of gifts or promotional aids to patients for the purpose of encouraging patients to request a particular medicine. Roche did not believe that, on the particular facts of this case, patients were encouraged to request a particular medicine from their consultant in breach of Clause 22 of the 2008 Code. Roche had, however, made sure that this principle was observed in all educational material now supplied to CF patients.

The material provided to patients was balanced and put the treatment in the context of the effects of the disease. As Roche had described, consultants initiated the enrolment of patients into the programme by contacting the agency after deciding to prescribe Pulmozyme. The programme only operated at the level of secondary care and, as would be expected at each clinic visit, usually six monthly, children would be subjected to careful and objective assessment of lung function. Appropriate treatment advice would then be given by the consultant or on his or her behalf and there would have been simply no opportunity for the fact that a patient was or was not enrolled in the programme to affect the prescriber's judgment. Neither would enrolment in the programme have caused patients to ask for a particular medicine because there was no alternative to Pulmozyme. It was the only medicine in its class, and it was indicated in nearly all CF patients, except a very small number who proved to be intolerant. The purpose of the programme was to encourage patients, mainly children, to take their medicine on a daily basis, once it had been prescribed. It was not intended, and did not, interfere in the decision to prescribe by influencing either the prescriber or patient in their choices. Roche believed that these specialists saw the programme as a positive contribution from Roche towards encouraging strict compliance in patients for whom compliance was critical.

Conclusion

In all of its actions concerning this programme Roche had taken its duty to act professionally and ethically and to uphold the high standards of the pharmaceutical industry very seriously. Roche believed it had discharged this duty and did not consider that the operation of the CF patient adherence and incentive programme had brought discredit to the pharmaceutical industry.

PANEL RULING

The Panel noted Roche's comments regarding the relevant Code and the timing of various activities. No new patients had been enrolled since September 2007 and the patient adherence and incentive programme had been finally stopped in September 2008. Arrangements which spanned

many years needed to be rechecked when changes to the Code were made. The letter to patients notifying them of changes and the closure of the programme was dated June 2007. Taking all the circumstances into account the Panel considered that the case would be considered under the 2006 Code using the 2008 Constitution and Procedure.

The Panel noted Roche's submission that daily adherence with Pulmozyme was particularly important in CF and that Pulmozyme was the only medicine in its class.

The Panel accepted that there were difficulties with adherence but did not consider the incentive scheme run by Roche was an appropriate means of encouraging patients to take their medicine. There was nothing about the scheme which ensured that patients took Pulmozyme as prescribed. The adherence programme booklet for patients included a section clearly labelled 'The Incentive'. The section labelled 'Your questions answered' mentioned the importance of taking Pulmozyme every day, whether there were symptoms or not. This was in line with the product's SPC.

The Panel noted that Roche representatives were given cycle goals (2004 and 2005) of recruiting patients to the adherence programme. Representatives were, according to Roche, initially financially rewarded on the number of patients enrolled. It was assumed that this would be by means of promoting the scheme to health professionals who would complete the enrolment form. The Panel was concerned that the scheme might have influenced the prescribing of Pulmozyme.

Roche submitted that it had instructed the agency to stop the incentive scheme by the end of September 2007. However this had not happened and vouchers continued to be sent out until the end of May 2008. This showed a serious lack of control by Roche.

The Panel was extremely concerned about the arrangements for many reasons. However it did not consider that the incentive scheme amounted to a gift, benefit in kind or pecuniary advantage given or offered to health professionals or administrative staff as an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. The benefit, in the form of vouchers for high street stores, was to patients not individual health professionals. The Panel thus ruled no breach of Clause 18.1.

The Panel did not consider that the vouchers were promotional aids as such. They were clearly linked to the use of the medicine. The supplementary information to Clause 18.2 stated that gifts to patients should be inexpensive and related to the condition under treatment or general health. Any such activity had to meet the requirements of the Code, in particular Clause 20. The Panel did not consider that vouchers for high street stores met this supplementary information. The Panel noted

that Clause 18.2 set out the requirements for promotional aids to health professionals. The vouchers were not promotional aids for health professionals and thus there could be no breach of Clause 18.2.

The Panel considered that gifts to patients was a difficult area. There was little guidance in the Code and little case precedent. However the Panel was very concerned about a pharmaceutical company in effect providing cash as an incentive to patients to use its medicine.

The Panel noted that Clause 20.2 required that statements should not be made for the purpose of encouraging members of the public to ask their health professional to prescribe a specific prescription only medicine. Clause 20.2 applied regardless of whether a patient was about to receive the first prescription of a particular medicine or was already regularly prescribed a particular medicine. The Panel considered that once enrolled into the programme, and knowing about the £10 vouchers, patients would be likely to ask their doctor to prescribe Pulmozyme and thus a breach of Clause 20.2 was ruled.

The Panel considered that the incentive scheme was totally unacceptable. It did not consider that Roche had maintained high standards. A breach of Clause 9.1 was ruled. The Panel considered that the arrangements brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel also considered that the incentive scheme for patients warranted consideration by the Code of Practice Appeal Board in relation to the possibility of additional sanctions. In addition the Panel was concerned that Roche's procedures had allowed vouchers to be distributed for over 6 months after the scheme had closed. The company was currently suspended from membership of the ABPI in relation to another matter. The Panel decided to report Roche to the Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

COMMENTS FROM ROCHE ON THE REPORT

Roche confirmed that the patient adherence programme was last fully operational in September 2007. No vouchers had been redeemed since June 2008 and a final letter reinforcing the closure of the scheme was sent in September 2008.

Roche was grateful for the guidance provided in the Panel's ruling in relation to items that might be provided to patients by way of incentives to compliance. As noted there had hitherto been little

guidance or case precedent in this area.

Whilst Roche did not appeal the Panel's rulings of breaches of the Code, it wanted to present to the Appeal Board in relation to the case and, in particular, to deal with any wider concerns that the Appeal Board might have about the scheme. The application of Clause 20.2 involved a judgement based upon the particular facts and, whilst Roche respected and understood the basis for the Panel's rulings, it was very clear that this particular scheme was very unlikely to have had adverse consequences for public health that outweighed its obvious benefits in terms of promoting compliance.

At the consideration of the report Roche provided correspondence from a consultant clinical psychologist with expertise in cystic fibrosis and a clinical director of a CF unit in support of its submission that no further sanctions be applied.

APPEAL BOARD CONSIDERATION

The Appeal Board noted the Panel's rulings in the case which were not appealed by Roche.

The Appeal Board accepted that daily treatment with Pulmozyme was particularly important in CF. Irrespective of whether or not the scheme complied with the Code, the Appeal Board was concerned that a patient adherence scheme was introduced with no means of measuring its effectiveness. The scheme was aimed at patients aged between eight and sixteen. The choice of voucher seemed odd given this age group.

The Appeal Board was extremely concerned that vouchers were still being distributed following Roche's decision to withdraw the programme in September 2007 and instructions to its agency at this time. This showed a serious lack of control by the company.

The Appeal Board noted that Roche was currently suspended from membership of the ABPI and undergoing a series of audits (Cases AUTH/2099/2/08 and AUTH/2100/2/08 and AUTH1819/4/06). The Appeal Board was very concerned about Case AUTH/2165/9/08 but decided that in the circumstances no further action was required in relation to possible further sanctions.

Complaint received	3 September 2008
Undertaking received	17 October 2008
Appeal Board consideration	13 November 2008

ASTELLAS PHARMA v PFIZER

Promotion of Toviaz

Astellas Pharma complained about the promotion of Toviaz (fesoterodine) by Pfizer. Pfizer also supplied Detrusitol (tolterodine).

The detailed response from Pfizer is given below.

Astellas stated that despite agreeing on 17 June to include Detrusitol prescribing information in Toviaz materials which contained claims about tolterodine, Pfizer distributed materials without the Detrusitol prescribing information at a national urology meeting, 23-27 June. This issue had already been the subject of Case AUTH/2130/6/08 about a Toviaz journal advertisement which referred to tolterodine but did not include the relevant prescribing information.

This demonstrated an unnecessary delay in withdrawing materials known to be in breach of the Code. Pfizer had told Astellas that it decided to withdraw materials without the necessary prescribing information too late to remove offending articles from the stand. Given that they were simply materials available for delegates to pick up, it would clearly have been possible simply to remove the offending items, and Astellas believed therefore that this behaviour demonstrated a cynical disregard for the Code and risked bringing discredit to the industry in breach of Clause 2.

The Panel noted that the lack of prescribing information on the materials at the Pfizer stand was covered by its ruling of a breach of the Code in Case AUTH/2130/6/08. The urology meeting had been held on 23-27 June. Although Pfizer acknowledged a breach in its response of 25 June, the company was not obliged to withdraw material until it accepted the Panel's ruling of a breach (10 July) following notification on 27 June. As the urology meeting was held at a time when Pfizer had yet to give its undertaking, it was not in breach of that undertaking to continue to use the material at issue. Such action was not outwith the Constitution and Procedure and thus no breach of Clause 2 was ruled. However given that Pfizer had acknowledged a breach of the Code, the Panel considered that it would have been helpful if the materials at issue had been removed from the stand. The Panel considered that although Pfizer had acted within the letter of the Code it queried whether it had acted within the spirit.

Astellas alleged that the claim 'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically, severe urgency with UUI [urgency urinary incontinence] per 24

hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours*' in a journal advertisement was not a balanced, fair and objective representation of the evidence available and hence was misleading. Astellas had repeatedly brought this issue to Pfizer's attention but had failed to reach an agreement. Astellas was particularly concerned that the claim was derived from a post hoc analysis. Further, the parameters at issue appeared to be a cherry-picked selection of both co-primary and secondary parameters from the original study.

The Panel noted that the claim at issue had been the subject of Case AUTH/2150/7/08, considered by the Panel and the Appeal Board. In Case AUTH/2150/7/08, the Panel noted that the study to which the claim was referenced (Chapple *et al* 2008) was a post hoc analysis of a phase 3 study by Chapple *et al* (2007). The original study had investigated the efficacy, tolerability and safety of Toviaz 4mg and 8mg vs placebo in overactive bladder (OAB). The study included a tolterodine ER 4mg arm as an active control. Both doses of Toviaz were significantly better than placebo in improving the symptoms of OAB. Efficacy was more pronounced with Toviaz 8mg than with other treatments. The post hoc study extracted from the original study only the data relating to Toviaz 8mg, tolterodine ER 4mg and placebo and examined the results for the primary endpoint (voids/24h), the two co-primary endpoints (UUI episodes/24h and treatment response), several secondary endpoints and health related quality of life (HRQoL). The data showed that by week 12 patients in both active-treatment groups showed significant improvements in most bladder diary variables and treatment response rates compared with placebo. Toviaz 8mg was statistically significantly better than tolterodine ER 4mg for improving UUI episodes, severe urgency plus UUI, mean voided volume and number of continent days/week. In addition the Toviaz and tolterodine groups showed significantly greater improvements in HRQoL than the placebo group. A major improvement in the severity of bladder-related problems was reported by 39% of the Toviaz group and 34% of the tolterodine ER groups v 25% of those on placebo ($p \leq 0.01$). The author stated that one of the limitations of the study was that it was a post hoc analysis of a study which was not powered for a comparison between active treatments or for HRQoL. Prospective studies were under way. The lack of consensus on measurement of the urgency classification was described as another shortcoming.

With regard to the second advertisement (TOV162)

the Panel noted that it was a well established principle under the Code that a claim could not be qualified by a footnote. It considered that given the statements in Chapple *et al* (2008) about the limitations of the study, the fact that it was a post hoc analysis and that Chapple *et al* (2007) was not powered for a between treatments comparison meant that the claim 'Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically...' was misleading and not capable of substantiation. Breaches of the Code had been ruled.

The position was further confused by the second part of the footnote 'Starting dose 4mg titrated up to 8mg for more efficacy'. This did not apply to Chapple *et al* (2007) where patients received medicine at the same dose throughout the study. It appeared to be more general information about the use of Toviaz as according to its summary of product characteristics (SPC) the recommended starting dose of 4mg once daily could, according to individual response, be increased to 8mg once daily (the maximum daily dose).

Overall, the Panel considered that high standards had not been maintained and a breach of the Code had been ruled.

Upon appeal by Pfizer of the Panel's rulings of breaches of the Code, the Appeal Board considered that the claim at issue, '... Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; ...' also referenced to Chapple *et al* (2008) implied statistical significance which was not so. The Appeal Board did not accept Pfizer's submission at the appeal that it was not claiming statistically significant superiority. There was a clear claim of superiority in the advertisement and this would be read as being clinically and statistically significant. The statistical analysis plan for Chapple (2008) had stated that the comparison of the two doses of Toviaz with tolterodine ER would only be done as an exploratory analysis and no p-values would be provided. Although a footnote stated 'Analysis of Toviaz 8mg v tolterodine ER was not part of the original study plan' otherwise misleading claims could not be so qualified. The Appeal Board considered that given the data upon which it was based, the claim was misleading and had not been substantiated. The Appeal Board upheld the Panel's rulings of breaches of the Code.

The position was further confused by a second footnote which stated 'Starting dose 4mg titrated up to 8mg for more efficacy'. This did not apply to Chapple *et al* where patients received Toviaz at the same dose (4mg or 8mg) throughout. It appeared that the footnote gave more general information about the use of Toviaz; according to its SPC the recommended starting dose was 4mg once daily which could, according to individual response, be increased to 8mg once daily (the maximum daily dose).

Overall, the Appeal Board considered that high standards had not been maintained and it upheld the Panel's ruling of a breach of the Code.

In the current case, Case AUTH/2167/9/08, the Panel considered that the previous rulings of breaches of the Code in Case AUTH/2150/7/08 applied here. The Panel considered that the comparison was misleading and a breach was ruled. The rational use of Toviaz was not encouraged and a breach was ruled.

In relation to the claim 'Toviaz is a new step in the treatment of Overactive Bladder', Astellas stated that Toviaz was an anti-muscarinic as were a number of currently available OAB treatments. Indeed the active metabolite of Toviaz was the same as that of tolterodine which had been available for many years, and the main difference between Toviaz and tolterodine was the route of metabolism. The term 'new step' inferred that Toviaz was either a completely new type of medicine for OAB, perhaps belonging to a new class or providing a new mechanism of action or administration, or provided an alternative way of treating the condition, rather than being an alternative anti-muscarinic adding to the choice of those available. Astellas did not consider that Toviaz offered a novel step or a breakthrough in the management of OAB. Astellas alleged that the claim was misleading as it implied that Toviaz had some special merit over other currently available treatments which it clearly had not.

The Panel considered that the phrase 'a new step' might be read as implying that Toviaz was a completely new approach for treating OAB. The claim appeared as a heading to two bullet points, the second of which was the claim comparing Toviaz and tolterodine ruled in breach above. According to Pfizer, Toviaz was metabolised to its active form by a different pathway compared with tolterodine (which had the same active metabolite). Toviaz was available in two doses unlike tolterodine. Pfizer submitted that Toviaz was a new step for Pfizer in the treatment of OAB. There was no claim for a novel step or breakthrough in management of OAB as alleged. The advertisement included a black triangle to denote that special reporting was required in relation to adverse events. Nonetheless, the Panel considered that the claim '... a new step...' implied more than just a new anti-muscarinic and in that regard it was misleading and could not be substantiated. Thus the Panel ruled breaches of the Code.

Astellas Pharma Ltd complained about the promotion of Toviaz (fesoterodine) by Pfizer Limited. Pfizer also supplied Detrusitol (tolterodine). Astellas supplied Vesicare (solifenacina). Astellas stated that inter-company dialogue had left three issues unresolved. Pfizer stated that it had worked closely and in a timely fashion to address the concerns of Astellas. However, additional information had been included in the complaint which it had not had the chance to discuss with

Astellas. No further details were provided in this regard.

This case was considered under the 2008 Constitution and Procedure. The clauses cited by Astellas, Clauses 2, 4.1, 7.2, 7.3, 7.4 and 7.10 were the same in the 2008 Code as in the 2006 Code.

1 Undertaking and withdrawal of material by Pfizer

COMPLAINT

Astellas stated that following agreement on 17 June that Detrusitol prescribing information should be included with materials which contained claims relating to tolterodine, Pfizer continued to distribute such materials on its stand at the British Association of Urological Surgeons (BAUS) Annual Meeting, Manchester, 23-27 June. This issue had already been the subject of a complaint (Case AUTH/2130/6/08) about a Toviaz journal advertisement which referred to tolterodine but did not include the relevant prescribing information. However, Pfizer continued to use materials on its stand at the BAUS conference with claims about tolterodine which did not contain the necessary prescribing information (ref TOV093) in breach of Clause 4.1.

This demonstrated an unnecessary delay in withdrawing materials known to be in breach of the Code. Pfizer had told Astellas that it decided to withdraw materials without the necessary prescribing information too late to remove offending articles from the stand. Given that they were simply materials available for delegates to pick up, it would clearly have been possible simply to remove the offending items, and Astellas believed therefore that this behaviour demonstrated a cynical disregard for the Code and risked bringing discredit to the industry in breach of Clause 2.

RESPONSE

Pfizer stated that it received a complaint from an anonymous GP on 10 June (Case AUTH/2130/6/08) regarding the omission of tolterodine prescribing information on a Toviaz advertisement (TOV097b), just prior to the complaint it received from Astellas on 13 June. Pfizer responded to the Authority on 25 June and accepted a breach of Clause 4.1 regarding another advertisement (TOV162). On 10 July Pfizer returned its undertaking that all materials would be corrected to ensure they were compliant. Pfizer had complied fully with this undertaking, and all materials which referred to tolterodine were subsequently updated to include the appropriate prescribing information.

PANEL RULING

The Panel noted that the lack of prescribing information on the materials at the Pfizer stand was

covered by its ruling of a breach of Clause 4.1 in Case AUTH/2130/6/08. The Panel noted that the BAUS meeting had been held on 23-27 June. Although Pfizer acknowledged a breach of Clause 4.1 in its response of 25 June, the company was not obliged to withdraw material until it accepted the Panel's ruling of a breach of the Code (10 July 2008) following notification on 27 June. As the BAUS meeting was held at a time when Pfizer had yet to give its undertaking, it was not in breach of that undertaking to continue to use the material at issue. Such action was not outwith the Constitution and Procedure and thus no breach of Clause 2 was ruled. However given that Pfizer had acknowledged a breach of Clause 4.1, the Panel considered that it would have been helpful if the materials at issue had been removed from the stand. The Panel considered that although Pfizer had acted within the letter of the Code it queried whether it had acted within the spirit.

2 Journal Advertisement (ref TOV162)

- a Claim 'By the end of treatment, Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically, severe urgency with UUI [urgency urinary incontinence] per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours**'

* Analysis of Toviaz 8mg vs tolterodine ER was not part of the original study plan

This claim was referenced to Chapple *et al*, article in press (Chapple *et al* 2008).

COMPLAINT

Astellas believed that this claim was not a balanced, fair and objective representation of the evidence available and hence was misleading. Astellas had repeatedly brought this issue to Pfizer's attention but had failed to reach an agreement. Astellas had asked an eminent statistician for an independent expert opinion on this claim in light of the current publicly available data. His report was provided.

Astellas alleged that the claim was in breach of Clauses 7.2, 7.3, 7.4 and 7.10.

- A post hoc analysis could not be used as the sole source of a claim, even if it was corrected for multiplicity. Findings from a post hoc analysis were exploratory and could not be considered as confirmatory in the absence of other relevant data. This claim appeared to be in breach of Clause 7.2.
- This claim originated from a post hoc analysis in which there was no multiplicity correction. In the referenced paper there was clear avoidance of specifying a sequential testing strategy in line with that used in the original study (Chapple *et al* 2007). If such a strategy was followed then no difference between Toviaz 8mg and tolterodine

4mg would have been observed (on change from baseline in micturition frequency) and thus no further tests would have been conducted. Therefore, the conclusion must be that this claim was not supported by a sound statistical basis and was in breach of Clause 7.2 (supplementary information).

- The parameters included in this claim, namely 'severe urgency with UUI per 24 hours, mean volume voided per micturition, continent days per week and UUI episodes per 24 hours', were only those which achieved an unadjusted p value of <0.05, and appeared to be a cherry-picked selection of both co-primary and secondary parameters from the original study. Astellas noted that there were four symptoms of overactive bladder (OAB): urgency, UUI, micturition frequency and nocturia. Only one of these symptoms was included in this claim. Regarding urgency, the claim referred only to those suffering from severe urgency, perhaps because there was no difference in overall urgency. Therefore the part of the claim referring to 'important endpoints' was misleading as three of the four key OAB symptoms were not included. This appeared, therefore, to be a breach of Clauses 7.3 and 7.4. The claim did not reflect all available evidence in breach of Clause 7.2. Furthermore, the failure to present all the evidence available such that the prescriber could make a rational decision about the use of Toviaz was in breach of Clause 7.10.

RESPONSE

Pfizer stated that it had updated its materials specifically relating to the claim at issue to make it clear which treatment endpoints had reached statistical significance.

Pfizer accepted a breach of Clause 7.2 for the previous advertisement TOV097b (Case AUTH/2150/7/08) as it agreed with the Authority that the claim 'Toviaz 8mg demonstrated improvements with statistical significance vs tolterodine ER 4mg in important treatment outcomes' could be viewed as too general.

Substantiation by post hoc analysis

Pfizer submitted that provided the materials clearly contained context information on the nature of the data, so as to ensure the reader was not misled, post hoc analysis could be used. This matter was currently under review by the Code of Practice Appeal Board (Case AUTH/2150/7/08).

The claim at issue stated that the significant improvements with Toviaz 8mg compared with tolterodine ER 4mg were relevant to a number of defined endpoints. These endpoints were then clearly specified, with no indication that this statistical significance related to all endpoints measured. Furthermore, a footnote was added to

provide further context on the analysis. The footnote ensured that the material was sufficiently complete to enable the reader to form their own opinion and did not qualify the claim.

Pfizer therefore did not agree that the claim was not substantiated by the referenced data or was misleading and was therefore not in breach of Clauses 7.2 or 7.4.

Statistical analysis

Although the statistical methods used in post hoc analysis might be similar to the primary methods used in a study, they did not necessarily follow the same approach regarding control for error rates. The closed-testing methodology used in the analysis of the three co-primary endpoints in the original Toviaz phase 3 trials was appropriate for controlling experiment-wise error rates. When performing post hoc analyses it was typical to report p values without adjustments, in order to help understand treatment differences separately, and not in the context of the overall error rate that also considered other comparisons. Generating individual comparison p values was an accepted and common practice in post hoc and secondary analyses.

Whilst the comparison of the two Toviaz doses to tolterodine ER was not the primary endpoint in the phase 3 trials, it was of clinical interest and had been pre-specified in the statistical analysis plan. The comparison was carried out on the full analysis set with the last observation carried forward, and the patient populations were not selected, altered or modified compared to that used for the pre-specified analyses.

The results for the co-primary endpoint urge incontinence showed that the 95% confidence interval for the treatment difference of 0.48 episodes/day between Toviaz 8mg and tolterodine ER 4mg was (-0.92; -0.05). Since this did not contain zero this indicated a difference between the two treatments with respect to urge incontinence.

The statistical methods used for the comparison of Toviaz 8mg with tolterodine ER were clearly described in the manuscript, which was accepted for publication following peer review and considered level 1b evidence by The British Journal of Urology International, a well respected, peer-reviewed journal.

Pfizer therefore did not agree that the claim was not substantiated by the referenced data, and therefore was not in breach of Clause 7.2.

Parameters included within claim

Toviaz and tolterodine were licensed for the treatment of symptoms of OAB syndrome which was defined as urgency, with or without urinary incontinence, often with frequency or nocturia. The parameters included in this claim – urgency,

incontinence and mean voided volume – were reported verbatim from the authors' published conclusions that these were important in the treatment of this condition and were three of five bladder variables that had been shown to be central to OAB.

Pfizer therefore did not agree that the claim at issue was in breach of Clauses 7.2, 7.3, 7.4 or 7.10.

PANEL RULING

The Panel noted that the claim at issue had been the subject of Case AUTH/2150/7/08, considered by the Panel and the Appeal Board as follows:

Case AUTH/2150/7/08

The Panel noted that the study to which the claim was referenced (Chapple *et al* 2008) was a post hoc analysis of a phase 3 study by Chapple *et al* (2007). The original study had investigated the efficacy, tolerability and safety of Toviaz 4mg and 8mg vs placebo in OAB. The study included a tolterodine ER 4mg arm as an active control. Both doses of Toviaz were significantly better than placebo in improving the symptoms of OAB. Efficacy was more pronounced with Toviaz 8mg than with other treatments. The post hoc study extracted from the original study only the data relating to Toviaz 8mg, tolterodine ER 4mg and placebo and examined the results for the primary endpoint (voids/24h), the two co-primary endpoints (urgency urinary incontinence (UUI) episodes/24h and treatment response), several secondary endpoints and health related quality of life (HRQoL). The data showed that by week 12 patients in both active-treatment groups showed significant improvements in most bladder diary variables and treatment response rates compared with placebo. Toviaz 8mg was statistically significantly better than tolterodine ER 4mg for improving UUI episodes, severe urgency plus UUI, mean voided volume and number of continent days/week. In addition the Toviaz and tolterodine groups showed significantly greater improvements in HRQoL than the placebo group. A major improvement in the severity of bladder-related problems was reported by 39% of the Toviaz group and 34% of the tolterodine ER groups v 25% of those on placebo ($p \leq 0.01$). The author stated that one of the limitations of the study was that it was a post hoc analysis of a study which was not powered for a comparison between active treatments or for HRQoL. Prospective studies were under way. The lack of consensus on measurement of the urgency classification was described as another shortcoming.

With regard to the second advertisement (TOV162) the Panel noted that it was a well established principle under the Code that a claim could not be qualified by a footnote. It considered that given the statements in Chapple *et al* (2008) about the limitations of the study, the fact that it was a post hoc analysis and that Chapple *et al* (2007) was not

powered for a between treatments comparison meant that the claim 'Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; specifically...' was misleading and not capable of substantiation. Breaches of Clauses 7.2 and 7.4 were ruled

The position was further confused by the second part of the footnote 'Starting dose 4mg titrated up to 8mg for more efficacy'. This did not apply to Chapple *et al* (2007) where patients received medicine at the same dose throughout the study. It appeared to be more general information about the use of Toviaz as according to its summary of product characteristics (SPC) the recommended starting dose of 4mg once daily could, according to individual response, be increased to 8mg once daily (the maximum daily dose).

Overall, the Panel considered that high standards had not been maintained and a breach of Clause 9.1 was ruled.

The Panel noted that Clause 2 was reserved as a sign of particular censure. It considered on balance that the circumstances did not warrant a ruling of a breach of that clause. This ruling was upheld by the Appeal Board upon appeal by the complainant.

Upon appeal by Pfizer of the Panel's rulings of breaches of the Code, the Appeal Board considered that the claim at issue, '... Toviaz 8mg was significantly better than tolterodine ER 4mg in improving a number of important endpoints; ...' also referenced to Chapple *et al* (2008) implied statistical significance which was not so. The Appeal Board did not accept Pfizer's submission at the appeal that it was not claiming statistically significant superiority. There was a clear claim of superiority in the advertisement and this would be read as being clinically and statistically significant. The statistical analysis plan for Chapple (2008) had stated that the comparison of the two doses of Toviaz with tolterodine ER would only be done as an exploratory analysis and no p-values would be provided. Although a footnote stated 'Analysis of Toviaz 8mg v tolterodine ER was not part of the original study plan' otherwise misleading claims could not be so qualified. The Appeal Board considered that given the data upon which it was based, the claim was misleading and had not been substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

The position was further confused by a second footnote which stated 'Starting dose 4mg titrated up to 8mg for more efficacy'. This did not apply to Chapple *et al* where patients received Toviaz at the same dose (4mg or 8mg) throughout. It appeared that the footnote gave more general information about the use of Toviaz; according to its SPC the recommended starting dose was 4mg once daily which could, according to individual response, be increased to 8mg once daily (the maximum daily dose).

Overall, the Appeal Board considered that high standards had not been maintained and it upheld the Panel's ruling of a breach of Clause 9.1. The appeal on this point was unsuccessful.

During its consideration the Appeal Board noted that the Toviaz SPC stated that 'The recommended starting dose is 4mg once daily. Based upon individual response, the dose may be increased to 8mg once daily. The maximum daily dose is 8mg'. The Appeal Board noted that in Chapple *et al* (2007) patients were started on either a 4mg or 8mg dose of Toviaz. The patients started on the maximum daily dose of 8mg Toviaz had not been treated in accordance with the Toviaz SPC.

Case AUTH/2167/9/08

The Panel considered that the previous rulings of breaches of Clauses 7.2 and 7.4 in Case AUTH/2150/7/08 applied here. With regard to the alleged breach of Clause 7.3 the Panel considered that the comparison was misleading and a breach was ruled. The rational use of Toviaz was not encouraged and a breach of Clause 7.10 was also ruled.

b Claim 'Toviaz is a new step in the treatment of Overactive Bladder'

COMPLAINT

Astellas stated that throughout much of its launch campaign Toviaz was claimed to be a 'new step' in the treatment of OAB. However, Toviaz was an anti-muscarinic as were a number of currently available OAB treatments. Indeed the active metabolite of Toviaz was the same as that of tolterodine which had been available for many years, and the main difference between Toviaz and tolterodine was the route of metabolism.

The term 'new step' inferred that Toviaz was either a completely new type of medicine for use in this disease area, perhaps belonging to a new class or providing a new mechanism of action or administration, or provided an alternative way of treating the condition, rather than being an alternative anti-muscarinic adding to the choice of those available. Astellas did not consider that Toviaz offered a novel step or a breakthrough in the management of OAB.

Astellas alleged that the claim was misleading in breach of Clauses 7.2, 7.3, 7.4 and 7.10 as it implied that Toviaz had some special merit over other currently available pharmaceutical agents for the treatment of OAB which it clearly had not.

RESPONSE

Pfizer believed that Toviaz might be described as a 'new step in the treatment of overactive bladder' because:

- it was a new anti-muscarinic, launched by Pfizer which currently manufactured the UK's leading OAB product, Detrusitol (tolterodine)
- it contained fesoterodine which was activated by ubiquitous esterases to its active metabolite the 5-hydroxymethyl (5-HMT) derivative. This was distinctly different from tolterodine which was metabolised to 5-HMT via hepatic metabolism.
- it was licensed in two doses 4mg and 8mg – this was a new step to those who were familiar with the single dose limitation of tolterodine.
- it was an anti-muscarinic as were a number of other compounds currently available for OAB. Despite the availability of these products, clinicians and patients still needed additional therapeutic options.

Pfizer therefore did not agree that the claim was misleading or suggested any special merit or quality (Clauses 7.2, 7.10) as Pfizer clearly stated it was a new anti-muscarinic. The materials relating to this claim did not make any comparative claims (Clause 7.3). The statement could be substantiated by its activation process and available doses and therefore was not in breach of Clause 7.10.

PANEL RULING

The Panel considered that the phrase 'a new step' might be read as implying that Toviaz was a completely new approach for treating OAB. The claim appeared as a heading to two bullet points, the second of which was the claim comparing Toviaz and tolterodine ruled in breach in point 2a above. According to Pfizer, Toviaz was metabolised to its active form by a different pathway compared with tolterodine (which had the same active metabolite, 5-HMT). Toviaz was available in two doses unlike tolterodine. Pfizer submitted that Toviaz was a new step for Pfizer in the treatment of OAB. There was no claim for a novel step or breakthrough in management of OAB as alleged. The advertisement included a black triangle to denote that special reporting was required in relation to adverse events. Nonetheless, the Panel considered that the claim '... a new step...' implied more than just a new anti-muscarinic and in that regard it was misleading and could not be substantiated. Thus the Panel ruled breaches of Clauses 7.2, 7.3, 7.4 and 7.10.

Complaint received 16 September 2008

Cases completed 14 November 2008

ROCHE v NOVARTIS

Zometa exhibition panel

Roche complained about the promotion of Zometa (zoledronic acid) by Novartis on an exhibition panel at the VII International Meeting on Cancer Induced Bone Disease 29 June – 2 July 2008.

The exhibition panel was headed 'Zometa reduces the risk of SREs [skeletal related events] more than any other bisphosphonate in advanced breast cancer'. The claim 'Intravenous zolendronate 4mg ... reduces rate of skeletal events, delays the time to a skeletal event, and significantly reduces the risk of developing a skeletal event' appeared above a Forest plot which depicted the overall risk of skeletal events in advanced breast cancer by individual medicines at recommended dosing. The Forest plot was adapted from Pavlakis *et al* (2005), a Cochrane Review on Bisphosphonates for Breast Cancer (2005). This review was subsequently republished with edits on 16 July 2008.

Roche alleged that the exhibition panel headed 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer' was inaccurate and unbalanced, misleading, incapable of substantiation and sought to disparage competitor products.

The original Cochrane diagram showed that the Zometa study was smaller than those with ibandronate and pamidronate. However, in the exhibition panel this diagram had been adapted so that all the studies appeared to contain a similar number of patients, in an attempt to misleadingly imply that they all carried the same weight.

The adapted diagram made no mention that it compared data from the reduction in risk of SREs for Zometa (an endpoint of events) with data derived from the reduction in skeletal morbidity period rate (SMPR) for ibandronate (an endpoint of time). Use of these different endpoints led to a perceived superiority in risk reduction for Zometa over ibandronate. However, elsewhere in the Cochrane report data were given for the same endpoint for these two medicines (skeletal event rate) and this showed a similar reduction in risk with both agents. Other publications also showed similar risk reductions for Zometa and ibandronate, when the same efficacy endpoint was used. Roche alleged that the exhibition panel did not give a fair and balanced view and it did not reflect all the evidence available. It made a misleading comparison between products, seeking to exaggerate the relative efficacy of Zometa in its class.

Roche alleged that the strapline 'Maintaining strength. Relieving pain' [which appeared beneath

the product logo in the right-hand bottom corner of the exhibition panel] was ambiguous and all-embracing. In inter-company dialogue during April and May 2008, Novartis had agreed that when using this strapline it would add references to studies which substantiated these features of Zometa. However, no references were attached to the strapline on the exhibition panel in Edinburgh, in breach of undertaking and of the high standards expected in promotion.

The detailed response from Novartis is set out below.

The Panel noted that the Cochrane review was a meta-analysis of 21 randomised studies which assessed the effect of bisphosphonates, as a class, on skeletal events, bone pain, quality of life and survival in women with early and advanced breast cancer. The primary outcome measure was the number of skeletal events. In nine studies compared with placebo or no bisphosphonates, bisphosphonates reduced SRE risk by 17%. This benefit was most certain with intravenous (iv) pamidronate 90mg, iv zolendronate 4mg and oral clodronate 1600mg. Bisphosphonates in women with advanced breast cancer without clinically evident bone metastases did not reduce skeletal event incidence. The overall conclusion was that in women with advanced breast cancer and clinically evident bone metastases, bisphosphonates reduced the risk of developing skeletal events and skeletal event rate as well as delaying the time to skeletal event.

When discussing implications for clinical practice the authors concluded *inter alia* that iv zolendronate (4mg every 3 to 4 weeks) was as effective as iv pamidronate (90mg), with regard to the risk of developing a skeletal event, skeletal morbidity rate, time to a skeletal event, pain and quality of life.

The Panel noted that Roche had alleged breaches of the Code in relation to the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer'. The company did not cite any reasons. Inter-company correspondence referred firstly to the absence of randomised controlled trials comparing the risk of SREs for Zometa versus clodronate or versus Bondronat; and secondly to the fact that the data presented in the Forest plot did not show the risk reduction for SREs for all the medicines and thus did not support the claim.

The Panel noted its concerns about the claim at issue set out below [final two paragraphs of the full

Panel ruling]. The Panel also queried whether the exhibition panel made it sufficiently clear that the study was a meta-analysis and there were no randomised controlled trials. The Panel noted that it had no allegation before it on these points. The Panel considered that Roche had made a narrow allegation about the principle of meta-analysis. The Panel noted that meta-analysis was an established and valid methodology particularly in the absence of head-to-head trials. However the claim was very strong. Readers might expect the supporting data to include randomised controlled comparative studies rather than a meta-analysis. There was in the Panel's view a claim for superior efficacy but there had been no complaint in this regard about the exhibition panel. The Panel did not consider that the absence of randomized controlled trials comparing Zometa with clodronate or Bondronat was alone sufficient to render the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate' in breach of the Code on the very narrow grounds alleged. No breach was ruled accordingly on this narrow point.

The Panel noted Novartis' submission that the data presented in the Forest plot were within each medicine's licence. The Panel had concerns about the exhibition panel nonetheless it did not consider that the failure to depict all presentations of medicines examined in the meta-analysis on the Forest plot rendered the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer' misleading, incapable of substantiation or disparaging on the very narrow ground alleged. Only licensed doses were depicted. No breach of the Code was ruled.

The Panel noted that the Forest plot was adapted from one published in 2005. The original Forest plot stated the sample size which was also reflected in the varying sizes of the accompanying boxes. Zometa 4mg had the smallest sample treatment size at 114 (control = 113) whilst iv pamidronate had the largest at 367 (treatment) and 384 (control). The exhibition panel did not reflect the sample size. Whilst p values and confidence intervals were given the Panel, nonetheless, considered the immediate impression created by the Forest plot on the exhibition panel was misleading on this point as alleged; a breach of the Code was ruled.

The Panel noted Roche's allegation that the Forest plot compared data from the reduction in risk of SREs for Zometa (an endpoint of events) and the skeletal morbidity rate for ibandronate (an endpoint of time). The Panel noted that the study section 'Data collection and analysis' stated that it relied for the primary outcome measure (number of skeletal events) on the total number of skeletal events reported in each paper. Authors were contacted for additional information that was not in the published trial to permit meta-analysis. The authors noted that the reporting of skeletal events and in particular the rate of events over time varied across the studies. Due to differences in the way outcomes were reported the study reported

survival and skeletal event data in two ways: as numbers of events and risk ratios and as ratios of event rates or time to an event. The Cochrane review stated that description and meta-analysis was restricted to those trials from which suitable data could be extracted. The Panel did not consider that the Forest plot was misleading, exaggerated or disparaging as the data was derived from different endpoints as alleged. The Cochrane paper addressed this issue. No breach of the Code was ruled on the narrow point alleged.

The Panel noted that the claim 'Maintaining strength. Relieving pain' appeared as a strapline beneath the product logo in the bottom right hand corner of the exhibition panel. The Zometa summary of product characteristics (SPC), pharmacodynamic properties explained that the selective action of bisphosphonates on bone was based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity was still unclear. In long-term animal studies zolendronic acid inhibited bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone. The Panel noted that any maintenance of bone strength was a consequence of Zometa's principal pharmacodynamic action, the inhibition of bone resorption. The Zometa SPC also discussed clinical trial results in the prevention of SREs in patients with advanced malignancies involving bone. In one trial patients receiving Zometa reported less increase in pain than those receiving placebo, and the difference reached significance at months 3, 9, 21 and 24. Another study reported showed that Zometa patients showed a statistically significant improvement in pain scores (using the Brief Pain Inventory) at 4 weeks and at every subsequent time point during the study when compared to placebo. The pain score for Zometa was consistently below baseline and pain reduction was accompanied by a trend in reduced analgesics score. The Panel did not consider the claim 'Maintaining strength. Relieving pain' ambiguous or all-embracing as alleged. The Panel considered that the exhibition panel was such that the claim at issue had been placed sufficiently within Zometa's licensed indication. No breach of the Code was ruled.

The Panel noted the parties' submissions about inter-company dialogue in relation to the allegation that the claim 'Maintaining Strength. Relieving Pain' should be referenced. The parties gave differing accounts of the agreement reached. The Panel considered that it was important that companies complied with agreements reached during inter-company dialogue. Such agreements should be clear. Nonetheless it was not a breach of the Code to fail to do so. Irrespective of any such agreement the Panel noted that there was no requirement under the Code to reference the claim in question. The claim had to be capable of substantiation, not misleading and otherwise comply with the Code. The Panel ruled no breach of the Code.

Roche Products Limited complained about the promotion of Zometa (zoledronic acid) by Novartis Pharmaceuticals UK Ltd on an exhibition panel at the VII International Meeting on Cancer Induced Bone Disease in Edinburgh, 29 June to 2 July 2008.

The exhibition panel was headed 'Zometa reduces the risk of SREs [skeletal related events] more than any other bisphosphonate in advanced breast cancer'. The claim 'Intravenous zoledronate 4mg ... reduces rate of skeletal events, delays the time to a skeletal event, and significantly reduces the risk of developing a skeletal event' appeared above a Forest plot which depicted the overall risk of skeletal events in advanced breast cancer by individual medicines at recommended dosing. The Forest plot was adapted from Pavlakis *et al* (2005), a Cochrane Review on Bisphosphonates for Breast Cancer (2005). This review was subsequently republished with edits on 16 July 2008.

Roche supplied Bonviva (ibandronic acid). Both medicines were bisphosphonates. Inter-company dialogue had left several issues unresolved.

The clauses cited in this complaint were the same in the 2008 as in the 2006 Code.

COMPLAINT

Roche summarised its concerns, detailed in inter-company dialogue, as follows:

- 1 Roche alleged that the exhibition panel headed 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer' was inaccurate and unbalanced, misleading, incapable of substantiation and sought to disparage competitor products, in breach of Clauses 7.2, 7.3, 7.4 and 8.1 of the Code.
- 2 The exhibition panel contained a diagram reproduced from the Cochrane Review of 2005, which purportedly substantiated the heading about SREs. The original Cochrane diagram showed that the Zometa study was smaller than those with ibandronate and pamidronate. However, in the exhibition panel this diagram had been adapted so that all the studies appeared to contain a similar number of patients, in an attempt to mislead the viewer that they all carried the same weight in breach of Clause 7.8.
- 3 The adapted diagram made no mention that it compared data from the reduction in risk of SREs for Zometa (an endpoint of events) with data derived from the reduction in skeletal morbidity period rate (SMPR) for ibandronate (an endpoint of time). Use of these different endpoints led to a perceived superiority in risk reduction for Zometa over ibandronate. However, elsewhere in the Cochrane report data were given for the same endpoint for these two medicines (skeletal event rate) and this showed a similar reduction in risk with both agents. Other publications also showed

similar risk reductions for Zometa and ibandronate, when the same efficacy endpoint was used. Roche alleged that the exhibition panel did not give a fair and balanced view and it did not reflect all the evidence available. It made a misleading comparison between products, seeking to exaggerate the relative efficacy of Zometa in its class, in breach of Clauses 7.2, 7.3, 7.8, 7.10 and 8.1.

- 4 The diagram misleadingly reproduced from the Cochrane report was also shown, by the chairman, in the Novartis-sponsored satellite symposium at the Edinburgh meeting. He stated that the graph demonstrated superior efficacy of Zometa versus other bisphosphonates which Roche alleged was also a breach of Clauses 7.2, 7.3, 7.4 and 8.1.
- 5 Roche alleged that the strapline 'Maintaining strength. Relieving pain' [which appeared beneath the product logo in the right-hand bottom corner of the exhibition panel] was ambiguous, all-embracing and in breach of Clauses 7.2 and 7.10. In inter-company dialogue during April and May 2008, Novartis had agreed that when using this strapline it would add references to studies which substantiated these features of Zometa. However, no references were attached to the strapline on the exhibition panel in Edinburgh, in breach of undertaking and of the high standards expected in promotion. Roche alleged a breach of Clause 9.1.

RESPONSE

Novartis stated that Roche had failed to comply with the 'Guidance on inter-company dialogue' produced by the Authority. Details were given.

Novartis explained that the Cochrane review aimed to review the efficacy of bisphosphonates on skeletal events (defined as any of new bone metastases, pathological fractures, spinal cord compression, irradiation of or surgery on bone, development or progression of bone pain). The authors commented on the heterogeneity in the reporting of skeletal event endpoints and in particular the rate of events over time. They stated that recent methodological reviews of 'multiple event reporting such as events per person per year', assumed constant event rates per patient in a given time period resulted in criticism of that method and had quoted a paper in support.

Cook and Major (2001), based on a substantial study of 380 patients with metastatic breast cancer, tested the validity of the 'events per person years' methodology. This was a commonly used technique for the analysis of SREs related over constant time periods. The authors concluded that this method of estimating SREs underestimated the variability in the data. This led to an unduly narrow confidence interval for complication rates (skeletal events) and inflated false positive error rates in treatment

comparisons. Therefore in conducting the meta-analysis, the Cochrane collaborative, defined as its main objective the assessment of efficacy using the total number of SREs reported in papers. In the event of insufficient information being reported in a paper, the authors were contacted for additional information pertinent to the review methodology.

Other papers also cited the primary results (skeletal event rates) of the Cochrane meta-analysis, giving further credibility to the need for such a study and of its conclusions. For example Aapro *et al* (2007), 'Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel' in which the table at the centre of this complaint was also reproduced. Aapro *et al* emphasised the overall risk reduction of skeletal events, as expressed by hazard ratios for each compound at currently licensed doses as a clinically relevant outcome.

According to the paper, Roche was given the opportunity together with all manufacturers of bisphosphonates, to comment on the manuscript. As far as Novartis was aware Roche had no objection to the use of this table, as the paper was now in the public domain in its final form.

Roche alleged that the exhibition panel headed 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer' was inaccurate and unbalanced, misleading, incapable of substantiation and sought to disparage competitor products, in breach of Clauses 7.2, 7.3, 7.4 and 8.1. In inter-company dialogue, the reason given was that there were no randomised controlled trials which compared the reduction in the risk of SREs for Zometa versus clodronate or versus ibandronate.

In the absence of comparative data derived from randomised controlled studies, the methodology employed by the Cochrane Collaborative in the form of meta-analysis, was a validated approach, with an *a priori* hypothesis which required strict criteria for studies to be eligible. These studies had to contain sufficient commonality (study design, patient population, similar intervention etc) for an indirect meta-analysis to be conducted. Meta-analysis was also used by the National Institute for Health and Clinical Excellence (NICE) and the Medicines and Healthcare products Regulatory Agency (MHRA) in conducting their reviews for the purpose of evaluation of medicines, licences, guidelines and guidances.

Novartis failed to see how the exhibition panel disparaged other competitors or their products. Studies that aimed to show relative differences in endpoints, where some of the products might show benefit did not disparage the remaining products. Roche had consistently alluded to breaches of Clause 8.1 in this and previous complaints. Novartis submitted this did not reflect the spirit of the Code nor did it become an organisation that should respect and adhere to the highest standards of

practice.

Novartis therefore maintained that in the absence of direct head-to-head studies, a meta-analysis was a valid and substantiated method by which to derive and present relative efficacies in a clinically meaningful way.

Roche stated that the exhibition panel contained a diagram reproduced from the Cochrane review, which purportedly substantiated the headline about SREs. The original Cochrane diagram showed that the Zometa study was smaller than those with ibandronate and pamidronate. However, in the exhibition panel this diagram had been adapted so that all the studies appeared to contain a similar number of patients, in an attempt to mislead the viewer that they all carried the same weight and in breach of Clause 7.8.

Whilst Novartis acknowledged that the boxes were of different sizes in the original report, the clear provision of confidence intervals, p values and relative risk reduction figures in the diagram prevented the misinterpretation of the data. When considering a Forest plot, absolute sample size was of statistically lesser importance than the p value, confidence intervals and distance from the equivalence line. These data had been presented accurately.

Novartis denied the exhibition panel was misleading.

Roche stated that the adapted diagram made no mention that it compared data from the reduction in risk of SREs for Zometa (an endpoint of events) with data derived from the reduction in SMPR for ibandronate (an endpoint of time) in breach of Clauses 7.2, 7.3, 7.8, 7.10 and 8.1.

The Cochrane review's primary outcome measure (number of SREs) relied on the total number of skeletal events reported in each paper, in preference to adding together each type of skeletal event. Roche was concerned that for studies whose primary endpoints were not skeletal events, such as SMPR, that data would need to be derived or manipulated in order to calculate the total skeletal event rates. The Cochrane review in its section 'Data collection and analysis' and 'Statistical analysis' explained how this bias was avoided. Studies were included in the review if they contained sufficient data on total skeletal events. If insufficient data was reported, authors were contacted to provide this information directly. Novartis therefore failed to see why Roche had raised this concern.

The Cochrane review provided data in two ways; as meta-analysis of plots/tables, as used in the exhibition panel and as ratios of event rates/times to events as in table 2 of the published paper. Roche had referred to this table in inter-company dialogue as a basis for its concern. Roche stated that these data suggested similar reductions in skeletal events for both Zometa and ibandronate contradicting the

results depicted in the exhibition panel.

Novartis submitted that this table was inappropriate to use in promotional materials as data within it was for unlicensed doses of some medicines. The data presented in the exhibition panel were for the relevant licensed doses of each medicine. Further, given the concerns highlighted by the Cochrane collaborative with respect to the accuracy interpreting results from certain time-related endpoints, Novartis again submitted that this was not the most appropriate table to use. In choosing the data it had adhered to both the Code and the MHRA's regulations on the 'Promotion of Medicinal Products'.

Roche also made inappropriate reference to other individual studies, as evidence that substantial data existed outside of this meta-analyses in comparing overall risk reduction for skeletal events for bisphosphonates. The objective of the Cochrane analysis was to fill this present knowledge gap. This was acknowledged by Roche.

Novartis therefore submitted that there was no basis for this concern.

In relation to Roche's allegation that the Forest plot was misleadingly reproduced from the Cochrane report and shown by the chairman in the Novartis-sponsored satellite symposium, Novartis believed that it had addressed this in previous comments in that the provision of comprehensive statistics (point estimates, confidence intervals, p values and relative risk reductions) shown in this presentation prevented the misinterpretation of data. In addition Roche was incorrect in its belief that the slide shown by the chairman had incorrect sample size boxes. Novartis provided a copy of the slide.

Novartis therefore submitted that there was no basis for this concern.

Use of the strapline 'Maintaining strength. Relieving pain' could not be interpreted as giving additional strength to muscle or providing a substantial analgesic effect as originally stated by Roche in inter-company dialogue. In Novartis' response it had mentioned that additional references would be added. Nowhere did this state that references would be added to the strapline in all materials, as Novartis believed clinicians experienced in the use of bisphosphonates would understand the intended meaning. Novartis had provided an example of promotional material where additional references had been included.

There was a substantial body of evidence both clinical and observational that attributed pain and pathological fractures to the process of malignant spread of cancers to bone. The malignant process involved both bone invasion by cancer deposits and subsequent erosion. This resulted in pathological fractures (SREs) which could be extremely painful and debilitating, requiring both medical and social support. The use of bisphosphonates reduced the

occurrence of pathological fractures by preventing the bone erosion (by reducing the activity of bone absorbing cells) therefore maintaining the bone matrix architecture and intrinsic strength.

Also important in the relief of pain by bisphosphonates was the action on osteoclasts (cells that absorbed bone) leading to their apoptosis (cell death). Pain associated with bone metastasis was considered to result from increased osteoclast activity. Osteoclasts degraded bone minerals by secreting protons through the vascular H⁺- ATPase, as such increased osteoclast activity was likely to lead to increased acidity in the local bone environment. This activated Acid-Sensing Ion Channel (ASIC) and Transient Receptor Potential Channel Vanilloid subfamily members leading to pain that was sometimes incapable of relief by analgesics. This gave a credible hypothesis as to why bisphosphonates might have an impact on pain in patients separate from the way more conventional analgesics worked.

Expert clinicians who specialised in cancer care, palliative care, orthopaedic surgery, radiotherapy, care of the elderly had considerable exposure to the use of this class of medicines. It was commonly accepted that bisphosphonates maintained bone strength and relieved the pain predominantly by preventing pathological fractures. The Cochrane review commented on the prevention of skeletal events and the reduction in pain. Draft NICE guidelines on 'Advanced Breast Cancer: Diagnosis and Treatment' also referred to the use of bisphosphonates in preventing fractures and their impact on pain. The Cochrane group conducted a further analysis of the use of bisphosphonates in prostate cancer in which the primary outcome under investigation was a reduction in pain.

Novartis therefore denied a breach of the Code.

* * * * *

The Director noted each party's submission about inter-company dialogue. Taking all the circumstances into account the Director decided that the requirements of Paragraph 5.2 had been satisfied, save in relation one allegation and thus this matter was thus not referred to the Panel.

* * * * *

PANEL RULING

The Panel noted that the Cochrane review was a meta-analysis of 21 randomised studies which assessed the effect of bisphosphonates, as a class, on skeletal events, bone pain, quality of life and survival in women with early and advanced breast cancer. The primary outcome measure was the number of skeletal events. In nine studies compared with placebo or no bisphosphonates, bisphosphonates reduced SRE risk by 17%. This benefit was most certain with intravenous (iv) pamidronate 90mg, iv zoledronate 4mg and oral

clodronate 1600mg. Bisphosphonates in women with advanced breast cancer without clinically evident bone metastases did not reduce skeletal event incidence. The authors' overall conclusion was that in women with advanced breast cancer and clinically evident bone metastases, bisphosphonates reduced the risk of developing skeletal events and skeletal event rate as well as delaying the time to skeletal event.

When discussing implications for clinical practice the authors concluded *inter alia* that iv zolendronate (4mg every 3 to 4 weeks) was as effective as iv pamidronate (90mg), with regard to the risk of developing a skeletal event, skeletal morbidity rate, time to a skeletal event, pain and quality of life.

The Panel noted that Roche had alleged breaches of Clauses 7.2, 7.3, 7.4 and 8.1 in relation to the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer'. The company did not cite any reasons but referred to inter-company correspondence for details of its allegations. The Panel noted that companies had previously been advised to submit a wholly separate and complete complaint to the Authority.

In a letter to Novartis, dated 7 August, Roche gave brief details about why it considered the claim at issue 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer' was in breach of the Code and referred firstly to the absence of randomised controlled trials comparing the risk of SREs for Zometa versus clodronate or versus Bondronat; and secondly to the fact that the data presented in the Forest plot did not show the risk reduction for SREs for all the medicines and thus did not support the claim.

The Panel noted its concerns about the claim set out below. The Panel also queried whether the exhibition panel made it sufficiently clear that the study was a meta-analysis and there were no randomised controlled trials. The Panel noted that it had no allegation before it on these points. The Panel considered that Roche had made a narrow allegation about the principle of meta-analysis. Novartis had responded accordingly. The Panel noted that meta-analysis was an established and valid methodology particularly in the absence of head-to-head trials. However the claim was a very strong claim. Readers might expect the supporting data to include randomised controlled comparative studies rather than a meta-analysis. There was in the Panel's view a claim for superior efficacy but there had been no complaint in this regard about the exhibition panel. The Panel did not consider that the absence of randomized controlled trials comparing Zometa with clodronate or Bondronat was alone sufficient to render the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate' in breach of Clauses 7.2, 7.3, 7.4 and 8.1 on the very narrow grounds alleged. No breach was ruled accordingly on this narrow point.

The Panel noted Novartis' submission that the data

presented in the Forest plot were for licensed doses lying within each medicine's licensed indication. The Panel had concerns about the exhibition panel nonetheless it did not consider that the failure to depict all presentations of medicines examined in the meta-analysis on the Forest plot rendered the claim 'Zometa reduces the risk of SREs more than any other bisphosphonate in advanced breast cancer' misleading, incapable of substantiation or disparaging on the very narrow ground alleged. Only licensed doses were depicted. No breach of Clauses 7.2, 7.3, 7.4 and 8.1 was ruled accordingly.

The Panel noted that the Forest plot was adapted from one published in the Cochrane Review 2005. The original Forest plot stated the sample size which was also reflected in the varying sizes of the accompanying boxes. Zometa 4mg had the smallest sample treatment size at 114 (control = 113) whilst iv pamidronate had the largest at 367 (treatment) and 384 (control). The exhibition panel did not reflect the sample size. The box for the smallest sample size, Zometa 4mg appeared in red at the top of the Forest plot and was a similar size to the black box for the largest sample size, pamidronate immediately beneath. Whilst p values and confidence intervals were given the Panel, nonetheless, considered the immediate impression created by the Forest plot on the exhibition panel was misleading on this point as alleged; a breach of Clause 7.8 was ruled.

The Panel noted Roche's allegation that the Forest plot compared data from the reduction in risk of SREs for Zometa (an endpoint of events) and the skeletal morbidity rate for ibandronate (an endpoint of time). The Panel noted that the study section 'Data collection and analysis' stated that it relied for the primary outcome measure (number of skeletal events) on the total number of skeletal events reported in each paper. Authors were contacted for additional information that was not in the published trial to permit meta-analysis. The authors noted that the reporting of skeletal events and in particular the rate of events over time varied across the studies. Due to differences in the way outcomes were reported the study reported survival and skeletal event data in two ways: as numbers of events and risk ratios and as ratios of event rates or time to an event. The Cochrane review stated that description and meta-analysis was restricted to those trials from which suitable data could be extracted. The Panel did not consider that the Forest plot was misleading, exaggerated or disparaging as the data was derived from different endpoints as alleged. The Cochrane paper addressed this issue. No breach of Clauses 7.2, 7.3, 7.8, 7.10 and 8.1 was ruled on the narrow point alleged.

The Panel noted that the claim 'Maintaining strength. Relieving pain' appeared as a strapline beneath the product logo in the bottom right hand corner of the exhibition panel. The Panel noted Novartis' submission that bisphosphonates reduced the occurrence of pathological fractures by preventing the bone erosion process thus

maintaining the bone matrix architecture and intrinsic strength. The Zometa summary of product characteristics (SPC), pharmacodynamic properties explained that the selective action of bisphosphonates on bone was based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity was still unclear. In long-term animal studies zolendronic acid inhibited bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone. The Panel noted that any maintenance of bone strength was a consequence of Zometa's principal pharmacodynamic action, the inhibition of bone resorption.

The Zometa SPC also discussed clinical trial results in the prevention of SREs in patients with advanced malignancies involving bone. In the first trial patients receiving Zometa reported less increase in pain than those receiving placebo, and the difference reached significance at months 3, 9, 21 and 24. The fourth study reported showed that Zometa patients showed a statistically significant improvement in pain scores (using the Brief Pain Inventory) at 4 weeks and at every subsequent time point during the study when compared to placebo. The pain score for Zometa was consistently below baseline and pain reduction was accompanied by a trend in reduced analgesics score. The Panel did not consider the claim 'Maintaining strength. Relieving pain' ambiguous or all-embracing as alleged. The Panel considered that the exhibition panel was such that the claim at issue had been placed sufficiently within Zometa's licensed indication. No breach of Clauses 7.2 or 7.10 was ruled.

The Panel noted the parties' submissions about inter-company dialogue in relation to the allegation that the claim 'Maintaining Strength. Relieving Pain' should be referenced. The parties gave differing accounts of the agreement reached. The Panel considered that it was important that companies complied with agreements reached during inter-company dialogue. Such agreements should be clear. Nonetheless it was not a breach of the Code to fail to do so. Irrespective of any such agreement the Panel noted that there was no requirement under the Code to reference the claim in question. The claim had to be capable of substantiation, not misleading and otherwise comply with the Code. The Panel ruled no breach of Clause 9.1.

The Panel was very concerned about the exhibition

panel. The prominent heading in a highlighted red band 'Zometa reduces the risk of SRE's more than any other bisphosphonate in advanced breast cancer' was a strong, unequivocal, comparative claim. It implied that statistically and clinically Zometa was better than the other bisphosphonates listed. The data beneath would be read in light of it. The Forest plot, depicting the overall risk of skeletal events in advanced breast cancer by individual medicine at recommended dosing showed zoledronic acid had the greatest risk reduction at 41%, $p=0.001$. The data was referenced to the Cochrane review, Pavlakis *et al* (2005) which examined bisphosphonates as a class. It was not designed to draw distinctions between any of the medicines studied contrary to the impression given by the exhibition panel. The Panel noted that whilst the Cochrane study authors commented favourably on individual Zometa studies they did not make a strong unequivocal statement in favour of the comparative efficacy of Zometa as inferred by the heading 'Zometa reduces the risk of SRE's more than any other bisphosphonate in advanced breast cancer' and the data beneath.

The Panel noted that the original Forest plot in the Cochrane review depicted the relative efficacy of each of the available bisphosphonates at their recommended doses compared with placebo or no bisphosphonate. It showed that Zometa achieved the greatest relative risk reduction compared to placebo or no bisphosphonates. Nonetheless the Panel did not consider that the heading was a fair reflection of the study authors' overall conclusions which were more equivocal. In this regard the Panel noted that the confidence intervals for Zometa and pamidronate almost completely overlapped. Nor did the Forest plot on the exhibition panel make it clear that it depicted the relative risk reduction of each bisphosphonate compared to placebo or no bisphosphonate. It was also unclear where the relative risk reduction of pamidronate at 23% ($p=0.00002$) depicted on the exhibition panel had come from. The Cochrane review referred to a relative risk reduction of 33%. The position was unclear. The Panel noted however that it had no complaint on these points and thus could make no ruling about them. The Panel considered that the parties should be advised of its views on this point.

Complaint received 19 September 2008

Case completed 12 January 2009

GE HEALTHCARE v BRACCO

Promotion of Niopam

GE Healthcare complained about the promotion of Niopam by Bracco using the IMPACT study (Barrett *et al* 2006) and alleged that pertinent information about its conduct, design and analysis had been omitted.

The study, entitled 'Contrast-Induced Nephropathy in Patients with Chronic Kidney Disease undergoing Computed Tomography: A double-blind comparison of Iodixanol and Iopamidol' aimed to 'prospectively compare the incidence of CIN [contrast induced neuropathy] after intravenous injection of equi-iodine doses of iopamidol-370 and iodixanol-320'.

A Bracco-sponsored webcast by one of the study's authors, described the IMPACT study as 'prospective, multi-centre, double-blind, randomised parallel groups'. Leaflets also sought to imply the prospective, randomised, controlled nature of this study.

The study was in fact the combination of data from two separate Bracco studies, VIRPACT and INVICTA. Contrary to the impression portrayed by the publication and the promotional materials, neither of these studies examined CIN as their primary endpoint. The primary objective of INVICTA was to examine image quality in patients undergoing peripheral vascular imaging with either iopamidol-370 or iodixanol-320. The primary objective of VIRPACT was to examine image quality in patients undergoing liver multidetector-row CT with either iopamidol-370 or iodixanol-320. Both studies had a secondary objective of examining CIN rates. These studies were only combined after patient recruitment was stopped, treatment and assessment were complete and statistical analyses underway and after the overall CIN rates of these studies could easily have been known.

GE Healthcare believed that neither the original publication nor promotional materials or activities stemming from this study accurately depicted its conduct. Additionally, the decision to combine data post-hoc, subsequent to collection of data endpoints and commencement of statistical analysis was of questionable validity. This breached the principles underpinning the conduct of clinical studies and brought discredit to the industry.

GE Healthcare alleged that Bracco's promotional materials omitted critical information on the conduct of the study, and were misleading and incapable of substantiation. Bracco's failure to maintain high standards breached the Code and risked bringing discredit to the industry in breach of Clause 2.

These concerns had been raised in inter-company correspondence, Bracco did not contest that IMPACT had pooled data from two earlier study protocols, one that had completed enrolment and the other that had been stopped. Rather it claimed that IMPACT was a prospective, multi-centre, double-blind, randomised, parallel group study which followed the best of clinical practice guidelines. GE Healthcare disagreed, as the IMPACT protocol was developed after patient enrolment had been completed, and after the patient data had been collected and a blinded analysis had been conducted.

The detailed response from Bracco is given below.

Certain of the allegations were not considered by the Panel because they had not been the subject of intercompany dialogue.

The Panel noted that the study concluded that the rate of CIN in patients with moderate-to-severe chronic kidney disease was similarly low after intravenous administration of equi-iodine doses (40g) of iopamidol-370 or iodixanol-320 for contrast-enhanced multi-detector computed tomography. The materials and methods section discussed the study patients, protocol and statistical analysis. It appeared to be one study designed *de novo* to assess the primary outcome measure. The discussion section stated that the results of the trial failed to demonstrate any difference in the incidence of CIN between equi-iodine doses of iodixanol-320 and iopamidol-370 for IV use in patients with pre-existing stable chronically reduced kidney function. The study authors noted that this was at odds with the findings of a previous trial comparing a nonionic monomer, iohexol with iodixanol but consistent with findings in other prospective or retrospective studies. It was noted that several previous studies had weaknesses which detracted from the IMPACT study authors' ability to reach valid conclusions. The study authors then described IMPACT as the largest prospective, randomized, double-blind comparison of iodixanol with a non-ionic monomer. Study limitations were discussed including calculation of the sample size which was based on the apparent differences between contrast agents in the NEPHRIC study (Aspelin *et al*, 2003). Whilst the number of subjects in IMPACT was higher (153 vs 129) the incidence of CIN observed was lower than anticipated. The IMPACT study authors noted that with the CIN incidence rates in the trial a study of about 3,800 cases would be required to detect even a 50% reduction in the incidence of CIN with one contrast medium over the other.

The Panel noted Bracco's submission that the prospective defining of patients, data and endpoints was entirely proper and the failure to mention the protocol amendments combining the data in, *inter alia*, related promotional material was completely irrelevant and would not affect readers' perception of the IMPACT data. The safety objectives and endpoints were the same in both studies. An expert on the Renal Safety Data Monitoring Board established by the IMPACT protocol confirmed that the board undertook a blinded review of data from INVICTA and VIRPACT to make the required determinations including eligibility. CIN rates were not known until the blind was broken for statistical analysis when the data from the two studies was combined. The protocols were identical with respect to CIN. There were no cases of CIN following iopamidol in either study; all of the very few cases of CIN occurred after iodixanol.

The Panel noted that GE Healthcare had provided a booklet entitled 'The Care Pathway Managing the Chronic Kidney Disease Patient in the Cardiology and Radiology Department'. A page headed 'Latest Clinical Evidence: The IMPACT Study' outlined the methodology from the published study and depicted the results in two bar charts. The first showed the percentage of patients with an increase in serum creatinine $\geq 0.5\text{mg/dL}$ from baseline (iopamidol-370, 0%, iodixanol-320, 2.6%; $p=0.30$). The second showed the percentage of patients with an increase in serum creatinine $\geq 25\%$ from baseline (iopamidol-370, 3.9%, iodixanol, 4%; $p=0.4$). An asterisked statement beneath the bar charts read 'The observed differences in CIN rates were not statistically significant ($p>0.05$)'. The Panel was concerned that the first bar chart gave the immediate visual impression of a statistically significant difference between the products whereas the study failed to demonstrate a difference.

The Panel noted that promotional material should be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and queried whether the reader had been provided with sufficient information about the study methodology to enable them to decide how much weight to attach to the data.

The Panel noted that the secondary endpoint data from two separate studies had been combined to become the primary endpoint in the IMPACT study. The material gave the impression that the CIN data was originally derived from a study wherein it was a primary endpoint. That was not so. The position was more complicated. The Panel also queried whether the study was sufficiently powered to detect a statistically significant difference. The Panel considered that on balance the failure to provide more information about the study methodology and sample size was a material omission and was misleading. A breach of the Code was ruled. The Panel did not consider that the material warranted a ruling of a breach of Clause 2

which was reserved to indicate particular censure.

GE Healthcare had also provided a branded summary of the study. This reproduced the data shown in bar charts referred to above and on a key message page stated 'The results showed a low level of CIN, with no significant difference observed between the two contrast agents'. The Panel queried whether stating that there was no significant difference observed between the products fairly reflected the fact that the study failed to demonstrate a difference between the products bearing in mind the authors' comments about the low incidence of CIN and that given this a study of about 3,800 would be required to detect a 50% reduction in the incidence of CIN. The Panel considered that its comments above also applied to the study summary. The Panel considered that on the balance of probabilities the omission of pertinent information was misleading as alleged. A breach of the Code was ruled. The Panel did not consider that the material warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure.

GE Healthcare complained about the promotion of Niopam (iopamidol) by Bracco UK Ltd. GE Healthcare marketed Visipaque (iodixanol)

COMPLAINT

GE Healthcare complained about the promotion of Niopam using the IMPACT study (Barrett *et al* 2006) and alleged that pertinent information about the conduct, design and analysis of this study had been omitted.

This study, entitled 'Contrast-Induced Nephropathy in Patients with Chronic Kidney Disease undergoing Computed Tomography: A double-blind comparison of Iodixanol and Iopamidol', was published in Investigative Radiology in 2006. The aim of the study was to 'prospectively compare the incidence of CIN [contrast induced neuropathy] after intravenous injection of equi-iodine doses of iopamidol-370 and iodixanol-320'.

A variety of materials from Bracco pursued this theme. For example, in a Bracco-sponsored webcast by one of the study's authors, the design of the IMPACT study was described as 'prospective, multi-centre, double-blind, randomised parallel groups'. Similarly, promotional materials such as leafpieces also sought to imply the prospective, randomised, controlled nature of this study.

IMPACT investigators had provided evidence that the study was in fact the combination of data from two separate Bracco studies, VIRPACT and INVICTA. Of significance, and contrary to the impression portrayed by the publication and the promotional materials, neither of these studies examined CIN as their primary endpoint. The primary objective of INVICTA was to examine image quality in patients undergoing peripheral

vascular imaging with either iopamidol-370 or iodixanol-320. The primary objective of VIRPACT was to examine image quality in patients undergoing liver multidetector-row CT with either iopamidol-370 or iodixanol-320. Both studies had a secondary objective of examining CIN rates. These studies were only combined after patient recruitment was stopped, treatment and assessment were complete and statistical analyses underway and after the overall CIN rates of these studies could easily have been known.

GE Healthcare believed that neither the original publication nor promotional materials or activities stemming from this study accurately depicted its conduct. Additionally, the decision to combine data post-hoc, subsequent to collection of data endpoints and commencement of statistical analysis was of questionable validity. Such actions breached the principles underpinning the conduct of clinical studies and brought discredit to the industry.

GE Healthcare alleged that Bracco's promotional materials omitted critical information on the conduct of this study, and therefore were misleading, incapable of substantiation in breach of Clauses 7.2, 7.4 and 7.10 of the Code. Furthermore, in this respect, Bracco's failure to maintain high standards breached Clause 9.1 and risked bringing discredit to the industry in breach of Clause 2.

These concerns had been raised in inter-company correspondence, Bracco did not contest that IMPACT had pooled data from two earlier study protocols, one that had completed enrolment and the other that had been stopped. Rather it claimed that IMPACT was a prospective, multi-centre, double-blind, randomised, parallel group study which followed the best of clinical practice guidelines. GE Healthcare disagreed, as the IMPACT protocol was developed after patient enrolment had been completed, and after the patient data had been collected and a blinded analysis had been conducted.

As it was unlikely that it would resolve this matter, GE Healthcare therefore deferred to the Authority for assistance. It asked that materials relating to IMPACT be withdrawn and that Bracco be required to communicate the material information that was omitted on the conduct of the study to the editorial board of *Investigative Radiology* and to clinicians with whom these data had been shared.

RESPONSE

Bracco stated that the allegations were groundless and false. It showed below and in an accompanying statement from an expert on the Renal Safety Data Monitoring Board established by the IMPACT protocol that IMPACT was a valid, prospective study that was conducted appropriately.

Bracco stated that it first learned of GE Healthcare's

intention to submit the complaint from a letter of 28 August that alleged, without any basis, that the IMPACT promotion was improper. In response, Bracco asked GE Healthcare to provide the basis for its allegations in a letter dated 9 September. GE Healthcare submitted this complaint, in which it essentially reiterated the baseless allegations from its 28 August letter. In doing so, not only did GE Healthcare fail to properly engage in inter-company dialogue as required under Paragraph 5.2 of the Constitution and Procedure, but it also added four new clauses of the Code that Bracco allegedly violated that were not specified in its 28 August letter. GE Healthcare also attempted to buttress its complaint with a misleading citation to a small and out-of-context piece of a very extensive record from a related litigation in the US.

By way of background, in December 2003 a Bracco-named entity filed a complaint against GE Healthcare in the US for false advertising. The decision in the case was still pending. Significantly, in that US litigation, the same allegations that GE Healthcare raised in this complaint were raised, and later dropped.

As explained below, contrary to GE Healthcare's allegations, the IMPACT study (Protocol IOP 107) was a prospective, randomised, double-blind, multicentre, parallel group study that followed all relevant clinical practice guidelines and resulted in a highly regarded, peer-reviewed journal article. The authors of the article and the investigators of the study were among the highest calibre and most prestigious researchers in the field. The prospective defining of patients, data and endpoints and the blinded combining of data from the VIRPACT and INVICTA studies to form IMPACT was entirely proper, and any failure to mention the protocol amendments combining the data in the IMPACT article or related promotional materials was completely irrelevant and would not affect readers' perception of the IMPACT data. As such, Bracco, did not believe the IMPACT article and related promotional materials were in breach of the Code.

VIRPACT and INVICTA were designed in early 2004 and began enrolment in November 2004. Both were prospective, randomised, double-blind, multicentre, parallel group studies sponsored by Bracco that compared the effects of iopamidol to iodixanol in patients with moderate-to-severe chronic kidney disease (serum creatinine stably equal or above 1.5mg/dL or a calculated creatinine clearance stably below 60ml/1.73 m²). The only difference between the two studies was that VIRPACT patients were examined with liver computed tomography (CT) whereas INVICTA patients were examined by CT angiography of peripheral vessels.

VIRPACT and INVICTA studied, *inter alia*, CIN, which was an acute decline in renal function after administration of an iodinated contrast medium. The possible difference in renal tolerability between iodixanol, an iso-osmolar contrast medium (IOCM)

and low-osmolar contrast media (LOCM, like iopamidol and others), was much debated after the publication of the NEPHRIC study, which was sponsored by GE Healthcare, and a massive promotional campaign by GE Healthcare aimed at convincing doctors that iodixanol, the LOCM, caused a lower rate of CIN than LOCM. The NEPHRIC study only compared iodixanol to a single LOCM – iohexol – in 129 patients. In its promotional campaign, GE Healthcare tried to claim that the NEPHRIC study results could be extrapolated to all LOCM (including iopamidol), not just iohexol.

At the time of VIRPACT, INVICTA and IMPACT, chronic kidney disease was known to be the most important factor for the development of CIN. Therefore, all the patients in the VIRPACT and INVICTA studies were at high risk of CIN.

VIRPACT and INVICTA were run in parallel and several of the investigational sites were involved with both studies. Of note:

- all patients in both studies received the same intravenous dose (40g of iodine) of either iodixanol or iopamidol, at the same injection rate, independently of the CT examination to be performed;
- the inclusion/exclusion criteria of the two studies were the same (with the type of CT examination they had to receive being the only difference);
- the randomization and blinding procedures were the same;
- the safety controls were exactly the same in both studies, including the controls for CIN (ie measurement of serum creatinine at screening, baseline and at 48-72 [hours] following the administration of the contrast media);
- the central laboratories used in the two studies were the same, as well as the procedures and methods for collection of blood samples, sample storage, sample shipment, and laboratory analysis;
- the safety objectives and endpoints were the same in both studies.

By mid-2005, it became apparent that although enrolment for VIRPACT was relatively steady, enrolment for INVICTA was extremely slow and was predicted to become even slower. This was because physicians increasingly believed that MR angiography was a safer alternative to CT angiography due to the lower dose of contrast required and of the lower risk of complications derived from the contrast-enhanced MR procedure. In November 2005, the INVICTA investigators suggested stopping recruitment, since it was very difficult to find new patients (only 45 of an expected 120 patients had been enrolled). Conversely, recruitment was almost complete for VIRPACT (in the end, 121 patients were recruited).

Since the safety and CIN controls were identical in VIRPACT and INVICTA, and CIN was a very important and sensitive issue, external experts and investigators recommended combining the two studies and prospectively focusing on CIN (see the expert's statement). In considering those recommendations, it was concluded by all concerned that combining the data would, at the very least, be the most ethical decision, to avoid simply stopping INVICTA and wasting the corresponding data (and also the risks to patients from exposure to the trial agents) that had been collected thus far. A new protocol was prepared, Protocol 107 (the IMPACT study), with CIN as the primary objective. The same CIN endpoint in the VIRPACT and INVICTA studies, ie an absolute post-dose increase in serum creatinine equal or above 0.5mg/dL, was used for the new sample size estimate, which was prospectively made and based on the results of the NEPHRIC study.

Of note, everybody involved in the studies (patients, investigators, external experts, sponsor representatives) was still blinded to the contrast agents used in individual patients and to the overall rates of CIN. No interim analyses were performed. Enrolment in VIRPACT was completed at the end of November 2005, and enrolment in INVICTA was stopped in December 2005. The new protocol of IMPACT was designed in November 2005, reviewed by the investigators in December 2005 and signed off and submitted to the ethics committees/institutional review boards in January 2006. A new, prospectively defined statistical analysis plan was defined in January 2006. Data management was started in January 2006.

According to the new IMPACT protocol, prior to unblinding any of the study data, completing data management and performing statistical analyses, a Renal Safety Data Monitoring Board comprising three medical experts was established: Each member of this Board was a licensed physician and an expert in contrast media safety and CIN. One was also a nephrologist, highly experienced in CIN studies and statistical analyses.

This board was responsible for reviewing the renal safety data and other necessary related data (eg demographics, medical history, concomitant medication) of each patient in a blinded manner, and validating each patient to be included in the study's renal safety analyses. The board was also responsible for following validation of the patients to be included in the renal safety analyses, database lock, unblinding, and statistical analyses of the renal safety data and reviewing the renal safety results of the study. The three members of the board were also in charge of the preparation of the study manuscript dealing with the CIN results. The manuscript was later published in *Investigative Radiology*, a peer-reviewed journal with the second highest impact factor in radiology (according to surveys of the field).

The review by the board was performed in February

2006. At the end of that review, 13 patients (7.8% of the entire study population) were not considered eligible for the primary CIN analysis. Before the end of that review, nobody could know the denominator to use to calculate CIN rates and the data were still blinded. Data management and statistical analysis were outsourced to a contract research organization. Data management completed in February 2006; the blind was broken after the database of the study was locked; and the statistical analysis was performed and completed between the end of February 2006 and March 2006. The first, draft results were circulated to all the investigators in March 2006. The manuscript was submitted to Investigative Radiology in June 2006.

The IMPACT study results showed a lower rate of CIN following the LOCM iopamidol than was expected from GE Healthcare's extrapolation of the NEPHRIC study. In the NEPHRIC study, using the same CIN endpoint (an absolute increase in serum creatinine equal or above 0.5mg/dL from baseline), the rates of CIN had been 3% following the IOCM iodixanol and 26% following the LOCM iohexol. In the IMPACT study those rates were zero (no cases of CIN) following the LOCM iopamidol and 2.6% following the IOCM iodixanol.

In response to GE Healthcare's allegations in the US litigation, Bracco retrospectively examined the IMPACT database and checked how many cases of CIN were observed in the original VERPACT and INVICTA patients. No cases of CIN occurred in the INVICTA population. Of the 121 patients in VIRPACT, 112 were considered eligible for the CIN analysis by the Renal Safety Data Monitoring Board. The rates of CIN in VIRPACT were again zero for the LOCM iopamidol and 3.6% following the IOCM iodixanol ie higher than the rate of CIN for iodixanol in IMPACT. This evidence supported Bracco's contention that there was no ulterior motive to combine the studies, since combination did not enhance the iopamidol data (in fact quite the contrary, as the rate of CIN reported in patients receiving the IOCM iodixanol was 3.6% in the INVICTA study and 2.6% when combined in the IMPACT study).

Of note, in the manuscript, at the section 'Study Limitations', the following was reported:

'The sample size of the study was calculated based on the apparent differences between contrast agents in the NEPHRIC study. While the number of subjects reported here is higher than that in the NEPHRIC study (153 vs. 129), the incidence of CIN observed was lower than anticipated in planning this trial. However, the 95% confidence interval around the difference in incidence of a 0.5 mg/L increase in SCr seen between trial groups ranges from -6.2% to 1.0%. Thus, our results are compatible with an absolute difference in CIN rates of close to 6% in favour of iopamidol or 1% in favour of iodixanol. With the CIN incidence rates seen in the current trial, a study of about 3800 cases would be required to detect even a 50% reduction in the incidence of

CIN with one contrast medium over the other.'

The incidence of CIN in VIRPACT and INVICTA were similar. Since: a) there were no cases of CIN following the LOCM iopamidol in either study; b) all (few) CIN cases were seen after iodixanol; and c) the power of VIRPACT or IMPACT alone would have been equally limited, the authors decided that it was irrelevant to mention the VIRPACT and INVICTA studies in any section of their manuscript (see the expert's statement).

In light of the above, GE Healthcare's allegations, ie that the studies 'were only combined after ... statistical analysis [was] underway' and 'after a blinded analysis had been conducted', and that 'the decision to combine data was post-hoc subsequent to ...commencement of statistical analysis' were completely false and had no support. The only support that GE Healthcare proffered for these statements were vague, highly selective statements that had been taken out of context, as set out in the expert's statement.

Contrary to the image that GE Healthcare attempted to paint, Bracco could have no improper commercial motive to avoid mentioning VIRPACT and INVICTA in its promotional materials. Indeed, if the studies had not been combined, as discussed above, Bracco could have possessed a study (VIRPACT) that showed even more remarkable trends of superiority of iopamidol over iodixanol.

Bracco did not believe that any of its promotional material breached any of the clauses of the Code. No reader would be misled by the absence of any reference to INVICTA and VIRPACT as IMPACT was a valid, reliable clinical study in its own right. Bracco was disappointed that GE Healthcare had chosen to repeat the allegation that the decision to combine the raw data from VIRPACT and INVICTA into the IMPACT study was only made '...after the overall CIN rates of these two studies could easily have been known'. Bracco made it crystal clear in the US litigation and repeated it here: the decision to combine the data might have led to Bracco forgoing an opportunity to claim a clinical superiority for its product over that of GE Healthcare. In the circumstances, the decision to combine the data was not a pre-meditated one based on commercial considerations.

For the reasons set forth above, Bracco requested that GE Healthcare's complaint be dismissed.

* * * * *

The Director noted Bracco's submission regarding inter-company dialogue. GE Healthcare set out its initial concerns in a letter dated 28 August wherein it expressed concerns regarding the promotion of iopamidol using the IMPACT study stating that pertinent information about the conduct, design and analysis of the study had been omitted. Promotional materials did not accurately depict its conduct. The study methodology was of questionable validity.

Further GE Healthcare alleged that such actions, *inter alia*, brought discredit to the industry and referred to Clause 2. The Director did not consider that a complaint to the Authority had to use identical language to that used in inter-company correspondence. It was important, however, that a formal complaint was not inconsistent with inter-company dialogue. New matters could not be raised in the complaint. On that basis the Director considered that inter-company dialogue had taken place in relation to Clause 7.2, and the allegation that the promotional materials did not accurately depict the study methodology and thus lacked pertinent information, and Clause 2. The complaint on these points was referred to the Panel for consideration. The alleged breaches of Clauses 7.4, 7.10 and 9.1 had not been the subject of intercompany dialogue and thus were not considered by the Panel.

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PANEL RULING

The Panel noted that the published study, Barrett *et al* stated that it compared the effects on renal function of iopamidol-370 injection and iodixanol-320 in patients with chronic kidney disease undergoing contrast-enhanced multi-detector computed tomography examinations using a multi-centre, double-blind, randomised parallel group design. The study concluded that the rate of CIN in patients with moderate-to-severe chronic kidney disease was similarly low after intravenous administration of equi-iodine doses (40g) of iopamidol-370 or iodixanol-320 for contrast-enhanced multi-detector computed tomography. The materials and methods section discussed the study patients, protocol and statistical analysis. It appeared to be one study designed *de novo* to assess the primary outcome measure. The discussion section stated that the results of the trial failed to demonstrate any difference in the incidence of CIN between equi-iodine doses of iodixanol-320 and iopamidol-370 for IV use in patients with pre-existing stable chronically reduced kidney function. The study authors noted that this was at odds with the findings of a previous trial comparing a nonionic monomer, iohexol with iodixanol but consistent with findings in other prospective or retrospective studies. It was noted that several previous studies had weaknesses which detracted from the IMPACT study authors' ability to reach valid conclusions. The study authors then described IMPACT as the largest prospective, randomized, double-blind comparison of iodixanol with a non-ionic monomer. Study limitations were discussed including calculation of the sample size which was based on the apparent differences between contrast agents in the NEPHRIC study (Aspelin *et al*, 2003). Whilst the number of subjects in IMPACT was higher (153 vs 129) the incidence of CIN observed was lower than anticipated. The IMPACT study authors noted that with the CIN incidence rates in the trial a study of about 3,800

cases would be required to detect even a 50% reduction in the incidence of CIN with one contrast medium over the other.

The Panel noted Bracco's submission that the prospective defining of patients, data and endpoints was entirely proper and the failure to mention the protocol amendments combining the data in, *inter alia*, related promotional material was completely irrelevant and would not affect readers' perception of the IMPACT data. The Panel noted Bracco's submission about the respective methodologies applied in the INVICTA and VIRPACT studies. The safety objectives and endpoints were the same in both studies. Bracco had submitted a statement from an expert on the Renal Safety Data Monitoring Board established by the IMPACT protocol. The expert confirmed that the board undertook a blinded review of data from INVICTA and VIRPACT to make the required determinations including eligibility. CIN rates were not known until the blind was broken for statistical analysis when the data from the two studies was combined. The expert statement explained that the protocols were identical with respect to CIN and noted that there were no cases of CIN following iopamidol in either study; all of the very few cases of CIN occurred after iodixanol; and the power of VIRPACT or IMPACT alone would have been equally limited.

The Panel noted that GE Healthcare had provided a booklet entitled 'The Care Pathway Managing the Chronic Kidney Disease Patient in the Cardiology and Radiology Department'. A page headed 'Latest Clinical Evidence: The IMPACT Study' outlined the methodology from the published study and depicted the results in two bar charts. The first showed the percentage of patients with an increase in serum creatinine $\geq 0.5\text{mg/dL}$ from baseline (iopamidol-370, 0%, iodixanol-320, 2.6%; $p=0.30$). The second showed the percentage of patients with an increase in serum creatinine $\geq 25\%$ from baseline (iopamidol-370, 3.9%, iodixanol, 4%; $p=0.4$). An asterisked statement beneath the bar charts read 'The observed differences in CIN rates were not statistically significant ($p>0.05$)'. The Panel was concerned that the first bar chart gave the immediate visual impression of a statistically significant difference between the products whereas the study failed to demonstrate a difference.

The Panel noted that promotional material should be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine and queried whether the reader had been provided with sufficient information about the study methodology to enable them to decide how much weight to attach to the data.

The Panel noted that the secondary endpoint data from two separate studies had been combined to become the primary endpoint in the IMPACT study. The material gave the impression that the CIN data was originally derived from a study wherein it was a primary endpoint. That was not so. The position

was more complicated. The Panel also queried whether the study was sufficiently powered to detect a statistically significant difference. The Panel considered that on balance the failure to provide more information about the study methodology and sample size was a material omission and was misleading. A breach of Clause 7.2 was ruled. The Panel did not consider that the material warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure.

GE Healthcare had also provided a branded summary of the study (BUK010621). This reproduced the data shown in bar charts referred to above and on a key message page stated 'The results showed a low level of CIN, with no significant difference observed between the two contrast agents'. The Panel queried whether stating that there was no significant difference observed

between the products fairly reflected the fact that the study failed to demonstrate a difference between the products bearing in mind the authors' comments about the low incidence of CIN and that given this a study of about 3,800 would be required to detect a 50% reduction in the incidence of CIN. The Panel considered that its comments above also applied to the study summary. The Panel considered that on the balance of probabilities the omission of pertinent information was misleading as alleged. A breach of Clause 7.2 was ruled. The Panel did not consider that the material warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure.

Complaint received **30 September 2008**

Case completed **19 December 2008**

SENIOR HOSPITAL NURSE/DIRECTOR v SYNER-MED

Ferinject brochure

A senior hospital nurse complained about a two page brochure 'Anaemia Service... Redesigning Provision' for Ferinjetc (ferric carboxymaltose) produced by Syner-Med.

The complainant stated that a colleague had obtained the brochure at a study day in Warwick on 19 September. After reading the brochure concerns were raised that iron had been administered incorrectly. The unit had given CosmoFer [a product marketed by Vitaline Pharma UK] on a second administration of 1,500mg over four hours yet the brochure stated 1,000mg over six hours. The brochure had caused unfounded anxiety and gave incorrect information as CosmoFer had been administered correctly.

The Authority noted that it appeared that the item at issue was identical to that ruled in breach in Case AUTH/2149/8/08 and so it asked Syner-Med to comment in relation to a possible breach of undertaking. It was the Authority's responsibility to ensure compliance with undertakings.

The detailed responses from Syner-Med are given below.

The Panel noted that in Case AUTH/2149/8/08 the brochure at issue had been ruled in breach of the Code as, *inter alia*, it was misleading to only refer to the infusion time for CosmoFer as 6 hours when the summary of product characteristics (SPC) stated that it could be administered over 4-6 hours. The Panel considered that its ruling in that case covered the complainant's allegation in the case now before it, Case AUTH/2170/9/08.

With regard to the undertaking given in the previous case, both parties agreed that the brochure had not been obtained from the company stand on 19 September. There was no evidence that the brochure had been supplied by Syner-Med after it had given its undertaking to withdraw it and thus there could be no breach in that regard.

A senior hospital nurse complained about a two page brochure 'Anaemia Service... Redesigning Provision' (ref F09/07-05-08-045) for Ferinjetc (ferric carboxymaltose) produced by Syner-Med (Pharmaceutical Products) Limited.

COMPLAINT

The complainant stated that a colleague had obtained the brochure at a study day in Warwick on

19 September. After reading the brochure concerns were raised that iron had been administered incorrectly. The unit had given CosmoFer [a product marketed by Vitaline Pharma UK] on a second administration of 1,500mg over four hours yet the brochure stated 1,000mg over six hours. The brochure had caused unfounded anxiety and gave incorrect information as CosmoFer had been administered correctly.

When writing to Syner-Med, the Authority asked it to respond in relation to Clause 7.2 of the Code. The Authority noted that it appeared that the item at issue was identical to that ruled in breach in Case AUTH/2149/8/08 and so it asked the company to comment in relation to Clause 25 which concerned breaches of undertakings. It was the Authority's responsibility to ensure compliance with undertakings.

RESPONSE

Syner-Med stated that on 18 August it undertook to withdraw, *inter alia*, the brochure at issue with immediate effect. Each hospital sales specialist was requested in writing to stop using the specified items immediately and to return all stock with a detail stock list. All stock of each item held at head office was immediately isolated and removed from the secure storage area to an off site lock-up pending destruction.

The local area hospital sales specialist attended the haematology study day held in Warwick on 19 September. The hospital sales specialist had confirmed that the brochure 'Anaemia Service, Redesigning Provision' was not available on the stand. He also confirmed that two previously unopened boxes of other brochures were opened at the venue, thus eliminating any risk of the box containing an incorrect brochure.

The company respectfully asked if the name of the complainant's colleague could be checked against the study day delegate list which was provided. It was possible that a health professional could have been given the detail aid at a meeting prior to 18 September.

The company had made every effort to ensure the detail aids in question had been recalled and destroyed and denied a breach of Clause 25.

The Authority asked Syner-Med to comment on the complainant's concerns and the complainant to name the colleague who had attended the study day.

FURTHER RESPONSE FROM SYNER-MED

Syner-Med stated that the CosmoFer summary of product characteristics (SPC) recommended that the total amount of CosmoFer, up to 20mg/kg bodyweight, was infused over 4-6 hours.

The brochure at issue compared the currently available iron products and the amount of time that it might take to administer 1,000mg of each. There had been no attempt to provide specific prescribing information regarding the minimum or maximum dosage for any product over a particular time and no attempt to provide specific prescribing information for individual patients.

The information regarding the administration of CosmoFer 1,000mg as a 6 hour infusion was correct and in line with its SPC.

The company was mindful that material should only provide meaningful comparisons between comparative pharmaceutical products when appropriate and should not replace an SPC to provide detailed prescribing information.

The company did not believe that it had provided incorrect or misleading information in breach of the Code or that the brochure at issue had been distributed after Syner-Med had given its undertaking to withdraw it, contrary to Clause 25.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that the colleague would not allow their name to be revealed and that the leaflet had been obtained from another person at the study day and not from the stand itself.

PANEL RULING

The Panel noted that in a previous case, Case AUTH/2149/8/08 the brochure at issue had been ruled in breach of Clause 7.2 as it was misleading to only refer to the infusion time for CosmoFer as 6 hours when the SPC stated that it could be administered over 4-6 hours. The Panel had also commented that any comparison of the different methods of administration for Ferinject and CosmoFer should make it abundantly clear as to which method and dose was being cited for each. The Panel considered that its ruling in the previous case covered the complainant's allegation in the case now before it, Case AUTH/2170/9/08.

With regard to the undertaking given in the previous case, both parties agreed that the brochure had not been obtained from the company stand on 19 September. There was no evidence that the brochure had been supplied by Syner-Med after it had given its undertaking to withdraw it and thus there could be no breach of Clause 25.

Complaint received **30 September 2008**

Case completed **12 November 2008**

VOLUNTARY ADMISSION BY ABBOTT

Synagis email

Abbott Laboratories voluntarily admitted that an email about Synagis (palivizumab), which one of its representatives had sent to a number of health professionals breached the Code. Synagis was indicated for the prevention of a serious lower respiratory tract disease requiring hospitalisation caused by respiratory syncytial virus (RSV) in children at high risk for RSV disease: children born at 35 weeks of gestation or less and less than 6 months of age at the onset of the RSV season; children less than 2 years of age treated for bronchopulmonary dysplasia within the last 6 months, and children less than 2 years of age with haemodynamically significant congenital heart disease.

Abbott explained that the email was sent as a follow-up to a meeting when the health professionals concerned had expressed an interest in being sent a link to a page on the Joint Committee on Vaccination and Immunisation (JCVI) website, which contained guidelines for the use of Synagis.

To this email, the representative attached a letter from a medicines management committee to the specialised commissioning lead for the paediatric network. This letter asked whether the various regional paediatric networks had reached consensus about the use of palivizumab and advised them that, until a consensus was reached, they should continue to support the policy (issued by a named regional group) recommending the use of palivizumab in premature neonates with chronic lung disease or congenital heart disease. This letter had been forwarded to Abbott by the assistant commissioning director for two primary care trusts with permission to pass it on to local health professionals to whom the advice was likely to be relevant.

Unfortunately, as well as the link to JCVI guidelines, the representative copied and pasted some text from the website, outlining the recommendations regarding palivizumab. Abbott considered this email would be perceived as promotional. It did not, however, have prescribing information attached and had not been formally certified. Similarly, the attached letter, which would also be classified by the Code as promotional when distributed in this manner, had not been certified and did not include prescribing information. Furthermore, the section of the JCVI guidelines reproduced within included a recommendation that palivizumab could be prescribed in children with severe immuno-deficiency which was not within the terms of the particulars listed in the summary of product characteristics (SPC).

The representative had confirmed that she had been given permission to email these customers. She copied in the lead pharmacist for acute commissioning in the region, as a courtesy, because the letter had been forwarded to Abbott by her assistant. She had not obtained permission from her to copy her into the email but did not feel this was necessary as she would already have been aware of the content.

The representative had been briefed specifically about the use of email; the briefing very clearly laid out the potential Code issues regarding emailing customers, and stressed that it was completely inappropriate to mention company products in any email of this nature. The representative had also recently passed refresher training on the Code that stressed the importance of certifying all promotional material. In the context of these briefings, Abbott believed that the representative had not maintained high standards.

Abbott stated that as a result of this incident it would rebrief all of its sales representatives reminding them of their responsibilities regarding the Code when it came to emailing with customers and reinforcing the importance of compliance in this regard.

Abbott submitted that although it had striven to maintain high standards throughout, it was impossible to fully regulate against an individual's lapse of judgement. The representative would shortly be the subject of internal disciplinary proceedings.

The Panel noted that the representative had been asked by a group of health professionals to provide a link to a page on the JCVI website which contained guidelines for the use of Synagis. To an email containing this information, entitled 'Funding availability and DoH Guidelines for Palivizumab', the representative had attached a copy of a letter from the chairperson of a medicines management committee to a specialised commissioning lead for the paediatric network entitled 'Palivizumab – Indications for RSV in neonates'. The Panel noted that although the representative had fulfilled a request her first responsibility was to act in accordance with the Code, regardless of customers' wishes to the contrary and the representative's intention to be helpful.

The Panel considered that the email and attached letter, given they had been sent by a representative with a commercial interest in palivizumab, clearly promoted the use of Synagis as acknowledged by Abbott. The material did not include prescribing

information and nor had it been certified. Breaches of the Code were ruled as acknowledged by Abbott.

The Panel noted that the email referred to the use of palivizumab in 'Children under 2 years of age with severe congenital immuno-deficiency'. This was outwith the licensed indications for Synagis. A breach of the Code was ruled as acknowledged by Abbott.

The Panel noted that the email had been sent to a group of health professionals who, according to the representative, had given their prior permission to be so contacted. No documentation had been provided to substantiate the representative's position. In this regard the Panel considered that companies must be very sure that health professionals had given their express permission for promotional materials to be emailed to them. The Panel noted, however, that the lead pharmacist for acute commissioning had been sent the email without her permission; it was irrelevant that the recipient was already aware of the content. A breach was ruled.

The Panel considered that the representative had not maintained a high standard of ethical conduct. A breach was ruled.

The Panel noted that a ruling of a breach of Clause 2 was reserved as a sign of particular censure. The supplementary information to Clause 2 stated that activities likely to be in breach of that clause included, *inter alia*, promotion prior to the grant of a marketing authorization and conduct of company employees/agents that fell short of competent care. The Panel considered that Abbott had been badly let down by its representative. However, given that the email had gone to a small group of health professionals who had asked for further information about local and national guidelines, that the reference to the use of palivizumab in an unlicensed group of children had reported verbatim the findings of a national expert advisory committee and the matter related to the misguided actions of one individual, the Panel decided, on balance, not to rule a breach of Clause 2.

Abbott Laboratories Limited voluntarily admitted that an email about Synagis (palivizumab), which one of its representatives had sent to a number of health professionals, was in breach of the Code. Synagis was indicated for the prevention of a serious lower respiratory tract disease requiring hospitalisation caused by respiratory syncytial virus (RSV) in children at high risk for RSV disease: children born at 35 weeks of gestation or less and less than 6 months of age at the onset of the RSV season; children less than 2 years of age and requiring treatment for bronchopulmonary dysplasia within the last 6 months, and children less than 2 years of age with haemodynamically significant congenital heart disease.

COMPLAINT

Abbott explained that the email was sent as a follow-up to a meeting on 25 July when the health professionals concerned had expressed an interest in being sent a link to a page on the Joint Committee on Vaccination and Immunisation (JCVI) website, which contained guidelines for the use of Synagis.

To this email, the representative attached an electronic copy of a letter from a medicines management committee to a specialised commissioning lead for the paediatric network. This letter asked whether the various regional paediatric networks had reached consensus about the use of palivizumab and advised them that, until a consensus was reached, they should continue to support the policy (issued by a named regional group) recommending the use of palivizumab in premature neonates with chronic lung disease or congenital heart disease. This letter had been forwarded to Abbott by the assistant commissioning director for two primary care trusts (PCTs) with verbal permission to pass it on to local health professionals to whom the advice was likely to be relevant.

Unfortunately, as well as the link to JCVI guidelines, the representative copied and pasted some text from the website, outlining the recommendations regarding palivizumab. Abbott considered this email would be perceived as promotional. It did not, however, have prescribing information attached and had not been formally certified. Similarly, the attached letter, even though it was not generated by Abbott and it had been given permission to circulate it to PCT customers, would also be classified by the Code as promotional, when distributed in this manner; it had not been certified, nor did it include prescribing information. Furthermore, the section of the JCVI guidelines reproduced within, included a recommendation that palivizumab could be prescribed in an indication (children with severe immuno-deficiency) that was not within the terms of the particulars listed in the summary of product characteristics (SPC). This recommendation was not mentioned in any of Abbott's promotional materials and should not have been passed on to customers in this manner.

Abbott considered that this email was in breach of Clauses 3, 4.1 and 14.1 of the Code.

In relation to Clause 9.9 the representative had confirmed that she had been given permission to email these customers. She copied in the lead pharmacist for acute commissioning in the region, as a courtesy, because the letter had been forwarded to Abbott by her assistant. She had not obtained permission from her to copy her into the email but did not feel this was necessary as she would already have been aware of the content enclosed.

The representative had been briefed specifically

about the use of email, on 14 June last year; the briefing very clearly laid out the potential Code issues regarding emailing customers, and stressed that it was completely inappropriate to mention company products in any email of this nature. The representative had also recently passed a Code refresher online training module (14 July) that stressed the importance of certifying all promotional material. In the context of these briefings, Abbott believed that the representative had not maintained high standards in breach of Clause 15.2.

Abbott stated that as a result of this incident it would rebrief all of its sales representatives reminding them of their responsibilities regarding the Code when it came to emailing with customers and reinforcing the importance of compliance in this regard.

Abbott submitted that it had striven to maintain high standards throughout and that, even when thorough precautions were taken to ensure Code compliance, it was impossible to fully regulate against an individual's lapse of judgement. The representative would shortly be the subject of internal disciplinary proceedings.

* * * *

Paragraph 5.4 of the Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. Issuing uncertified material and promoting medicines outwith their marketing authorization were serious matters and the admission was accordingly treated as a complaint.

When writing to Abbott the Authority asked it to respond in relation to Clauses 2, 3.1, 4.1, 9.1, 9.9, 14.1 and 15.2.

RESPONSE

Abbott explained that at various recent meetings, local clinicians expressed an interest, to one of its representatives, in obtaining further information relating to local and national guidance on the use of palivizumab. They specifically requested a link to the website on which the JCVI had published its recommendations on the use of palivizumab in the prevention of RSV infection in young children. The representative was also asked for a copy of a letter from a medicines management committee (to a specialised commissioning lead for the paediatric network) which contained advice to regional paediatric networks on policy regarding the use of this treatment. This letter had been forwarded to Abbott by the assistant commissioning director for two PCTs with verbal permission to pass it on to those clinicians to whom the advice was likely to be relevant.

The letter advised the local networks that, until a

consensus was reached, they should continue to support the policy (issued by a named regional group) recommending the use of palivizumab only in the treatment of premature neonates with chronic lung disease or congenital heart disease.

To put the advice contained within this letter in context, Abbott noted that these recommendations restricted the use of palivizumab to a cohort of patients that was significantly smaller than the licensed indications for the product – which allowed palivizumab to be used in all children under two years of age who had chronic lung disease or haemodynamically significant congenital heart disease, as well as all premature neonates, who were less than 6 months old at the start of the RSV season, whether or not they had heart or lung disease. As a result, the representative's proactive distribution of this letter facilitated the distribution of existing information to the clinicians involved but would not serve any other commercial purpose and could, if anything, restrict the use of palivizumab in the region. The representative now realised she should not have involved herself in the distribution of this information within this group of clinicians and left this role to someone within the NHS.

The JCVI recommendations were published in 2004 as a result of the formal review of the findings of a separate expert group meeting, held in 2002. The JCVI was an independent expert advisory committee set up by the Department of Health (DoH). The published recommendations, issued in 2004 and documents on the JCVI website – the web address of which had been requested from its representative – were as follows:

'The following children should be recommended for palivizumab prophylaxis

- Children under 2 years of age with chronic lung disease, on home oxygen or who have had prolonged use of oxygen
- Infants less than 6 months of age who have left to right shunt haemodynamically significant congenital heart disease and/or pulmonary hypertension
- Children under 2 years of age with severe congenital immuno-deficiency.'

Palivizumab was not licensed for the treatment of infants with congenital immuno-deficiency. For this reason, Abbott did not reproduce the third bullet point in promotional materials and it accepted that the inclusion of these recommendations, in full, would be construed as promoting outside of the terms of the marketing authorization. However, the intention behind giving clinicians these recommendations was to facilitate the provision of information to those who had expressed an interest in locating these independent guidelines.

When considering this complaint, Abbott asked the Authority to take into account the intention behind the email which was that of a genuine desire to provide these clinicians with independently produced materials, which had been generated

specifically for this audience and which had been verbally requested by everyone to whom the email was addressed.

The company, however, accepted that the text which was copied and pasted from the JCVI website constituted a breach of Clause 3, as discussed above, albeit regarding use of the product in line with national recommendations published on behalf of the DoH.

Abbott also accepted that the inclusion of its product name within the attached letter and the email, meant that the communication was promotional material in its own right. Prescribing information was not provided and the material had not been certified and, as such, was in breach of Clauses 14.1 and 4.1.

Abbott did not believe this email represented a breach of Clause 9.9 because the representative concerned had confirmed that she had been given permission to email these customers.

With regard to Clauses 9.1 and 15.2, the company noted that it strove to ensure that a culture of high standards and compliance were central to all of its activities. Every affiliate had been asked to focus on 'core values', which should underpin its behaviour in every aspect of the business. Abbott's mission statement included the following advice 'We strive to earn the trust of those we serve by committing to the highest standards of quality, excellence in personal relationships, and behaviour characterized by honesty, fairness and integrity'. Abbott provided details of its ongoing compliance programme.

Abbott stated that whilst the actions of this individual representative were unacceptable, it took the training of its representatives, with regard to Code compliance, extremely seriously. Details of the representative's training on the Code, and the successful completion of various modules, was provided.

All Abbott representatives were trained on the Code and received regular briefings to remind them of their responsibilities regarding the Code, as required. The representative briefing provided to its sales force, which was most relevant to this complaint, discussed the use of uncertified material (with specific reference to email) and discussion of off-liscence indications.

This briefing contained the following guidance relating to email:

'Representatives may only initiate or engage in correspondence (by any means eg email, text message, fax etc) with health professionals and relevant administrative staff if all of the following are true:

- Prior permission is given by the recipient
- The content does not mention any pharmaceutical product by name (trade or generic)

- The content does not refer in any way to a pharmaceutical product (eg its use or its properties etc)...'

The same briefing provided the following guidance relating to uncertified materials:

'... therefore it is important understand that:

- Representatives may not initiate or engage in any correspondence concerning a pharmaceutical product (even if the product is not mentioned by name)
- Representatives may not initiate or engage in any correspondence with the purpose of promoting a product
- Under the ABPI Code of Practice no promotional material can be sent/used/issued/distributed by representatives until it has been certified by company signatories in accordance with Clause 14 of the Code...'

Finally the briefing provided the following guidance, regarding off-liscence indications:

'... a sales representative's activities are perceived as promotional in nature. If there is any discussion relating to data on the use of any medicine in an indication for which it does not yet have a license it will be construed as promotion, and hence, a breach of the Code of Practice (Clause 3).

The briefing concluded with the following warning:

'Abbott as a company strives to live by its values – Pioneering, Achieving, Caring and Enduring – through the actions and behaviours of all of us. Setting high standards is a foundation on which we base our behaviours. Breaches of the ABPI Code of Practice are taken extremely seriously and are a disciplinary matter.'

In view of this complaint, additional 'face to face' training regarding the Code would be implemented across the entire sales force to further reinforce the messages that the company instilled in its sales representatives from their induction onwards. This would include where it might be more appropriate for a representative to decline to be the distributor of information that might have been requested by attendees of meetings.

In view of the ongoing compliance activities of the organisation, the extensive training this individual received and the specific guidance issued – relating to the issues that were central to this case – Abbott submitted that it had maintained high standards throughout and that every effort had been taken to ensure Code compliance. As soon as the company became aware of this matter, it conducted a full internal investigation and as a result of that investigation, it voluntarily reported this issue to the Authority, as well as completing formal disciplinary proceedings against the individual concerned.

Abbott therefore accepted the actions of this

individual representative were in breach of the Code, specifically Clauses 3, 9.9, 15.2, 14.1 and 4.1. Abbott, however, believed that it had maintained high standards throughout and it believed that its actions since had been entirely appropriate and were not likely to reduce confidence in the pharmaceutical industry, nor had the representative actions prejudiced patient safety or public health. Abbott therefore did not consider that a breach of Clause 9.1 or of Clause 2 was appropriate.

PANEL RULING

The Panel noted that the representative had been asked by a group of health professionals to provide a link to a page on the JCVI website which contained guidelines for the use of Synagis. To an email containing this information, entitled 'Funding availability and DoH Guidelines for Palivizumab', the representative had also attached a copy of a letter from the chairperson of a medicines management committee to a specialised commissioning lead for the paediatric network entitled 'Palivizumab – Indications for RSV in neonates'. The Panel noted that although the representative had fulfilled a request her first responsibility was to act in accordance with the Code, regardless of customers' wishes to the contrary and the representative's intention to be helpful.

The Panel considered that the email and attached letter, given they had been sent by a representative with a commercial interest in palivizumab, clearly promoted the use of Synagis as acknowledged by Abbott. The material did not include prescribing information and nor had it been certified. Breaches of Clauses 4.1 and 14.1 were ruled as acknowledged by Abbott.

The Panel noted that the email referred to the use of palivizumab in 'Children under 2 years of age with severe congenital immuno-deficiency'. This was outwith the licensed indications for Synagis. A breach of Clause 3.1 was ruled as acknowledged by

Abbott.

The Panel noted that the email had been sent to a group of health professionals who, according to the representative, had given their prior permission to be so contacted. No documentation had been provided to substantiate the representative's position. In this regard the Panel considered that companies must be very sure that health professionals had given their express permission for promotional materials to be emailed to them. The Panel noted, however, that the lead pharmacist for acute commissioning had been sent the email without her permission; it was irrelevant that the recipient was already aware of the content. A breach of Clause 9.9 was ruled.

The Panel considered that the representative had not maintained a high standard of ethical conduct. Breaches of Clauses 9.1 and 15.2 were ruled.

The Panel noted that a ruling of a breach of Clause 2 was reserved as a sign of particular censure. The supplementary information to Clause 2 stated that activities likely to be in breach of that clause included, *inter alia*, promotion prior to the grant of a marketing authorization and conduct of company employees/agents that fell short of competent care. The Panel considered that Abbott had been badly let down by its representative. However, given that the email had gone to a small group of health professionals who had asked for further information about local and national guidelines, that the reference to the use of palivizumab in an unlicensed group of children had reported verbatim the findings of a national expert advisory committee and the matter related to the misguided actions of one individual, the Panel decided, on balance, not to rule a breach of Clause 2.

Proceedings commenced	6 October 2008
Case completed	18 November 2008

BOEHRINGER INGELHEIM v BAYER SCHERING PHARMA

Promotion of Xarelto

Boehringer Ingelheim complained about Bayer Schering Pharma's promotion of its anticoagulant Xarelto (rivaroxaban). Boehringer Ingelheim supplied Pradaxa (dabigatran).

Given the dates of the activities in question the Panel decided to use the provisions of the 2006 Code using the 2008 Constitution and Procedure. The clauses at issue had not changed under the two Codes but some had been renumbered.

The detailed responses from Bayer Schering are given below.

Boehringer Ingelheim alleged that at the Irish Orthopaedic Association meeting, Belfast, in June 2008, Bayer Schering had an exhibition stand on venous thromboembolism which stated 'Great Clinical Need for New Anticoagulants...' and then described various desirable attributes. The stand was manned by sales representatives and marketing team members. Boehringer Ingelheim was concerned that having the stand would solicit questions on the availability of new anticoagulants and that questions would be answered by sales representatives, promoting the medicine prior to the receipt of the marketing authorization. The stand did not mention that the new anticoagulant Pradaxa (dabigatran) with this profile was available. Boehringer Ingelheim alleged that this was disparaging and misleading. Boehringer Ingelheim noted that Bayer Schering had distributed a leaflet entitled 'Thrombosis Adviser' and a two question quiz card on deep vein thrombosis and the characteristics of an ideal anticoagulant. The quiz offered entry into a draw to win a book voucher which Boehringer Ingelheim alleged was in breach of the Code.

The Panel noted that the material had been supplied by Bayer Schering's Irish affiliates. As the meeting took place in the UK, the UK Code applied.

The Panel noted that one of the exhibition panels at issue referred to VTE (venous thromboembolism) as a seriously underestimated killer. The second exhibition panel was headed 'Great Clinical Need for New Anticoagulants Providing: effective anticoagulation; low risk of bleeding; oral delivery; wide therapeutic window; fixed dosing; no monitoring; low risk of food and drug interactions and predictable pharmacology'. The Panel considered that the second exhibition panel, given the context in which it was used, ie a promotional exhibition space, in effect promoted Xarelto in June 2008 prior to the grant of its marketing authorization on 1 October 2008. The exhibition panel listed Xarelto's benefits; it would be clear to

delegates that Bayer Schering had a commercial interest in an oral anticoagulant with the profile listed. A breach was ruled.

The Panel considered that the heading to the second exhibition panel 'Great Clinical Need for New Anticoagulants Providing:' ignored the fact that Boehringer Ingelheim's new anticoagulant (Pradaxa) was already available. The heading implied that no anticoagulant was available with the properties listed which was not so. The Panel noted Bayer Schering's submission that the unmet need referred to therapy areas other than preventing VTE following orthopaedic surgery. This was not made clear on the exhibition panel. The Panel considered that the exhibition panel was misleading and disparaging as alleged. Breaches of the Code were ruled.

The Panel noted that a leaflet distributed from the exhibition stand had asked delegates to 'Test your knowledge on VTE and enter a draw to win a book voucher'. The supplementary information to Clause 18.2 of the 2006 Code stated 'The use of competitions, quizzes and suchlike, and the giving of prizes, are unacceptable methods of promotion'. A breach was ruled as alleged.

With regard to a supplement on rivaroxaban in the Journal of Bone and Joint Surgery (JBJS), Boehringer Ingelheim noted that the journal was available on 4 September 2008 prior to the grant of the marketing authorization for rivaroxaban.

The supplement was funded by Bayer Schering as stated in the acknowledgements of each article. However, there was no clear mention of the sponsor company at the outset.

Boehringer Ingelheim alleged that the statement 'An introduction to rivaroxaban: the first oral, once-daily, direct Factor Xa inhibitor for the prevention of venous thromboembolism' was misleading as it implied that rivaroxaban was available in September 2008 for prescription.

A statement, 'Rivaroxaban offers clinicians and their patients a novel orally active anticoagulant for extended thromboprophylaxis in the outpatient setting' was alleged to be misleading and promotion prior to the grant of the marketing authorization as 'offers' was in the present tense.

The claims 'Rivaroxaban will offer clinicians the opportunity....' and 'Importantly, unlike parenteral anticoagulants, rivaroxaban will enable an easy transition...' implied that rivaroxaban would work for all patients which was alleged to be

misleading and exaggerated. In addition, Boehringer Ingelheim considered that these claims implied that rivaroxaban would definitely be available which, given that rivaroxaban was not licensed at the time of publication, was in breach of the Code.

The graph 'Efficacy of *currently* available options for venous thromboprophylaxis' (emphasis added) did not include dabigatran which had a marketing authorization for primary prevention of venous thromboembolism events in adults following elective total hip or knee replacement surgery and was available in the UK. Boehringer Ingelheim alleged that the graph did not reflect up-to-date evidence and was misleading.

The Panel noted that the objective was to provide the proceedings of a symposium, sponsored by Bayer Schering at an international meeting, in the form of a journal supplement. The Panel considered that it would not always be possible to achieve this and comply with the requirements of the Code.

The Panel noted that the supplement had been initiated by Bayer Schering and its agency. The co-editors and first authors were those who had taken part in the company-sponsored symposium at EFORT 2008 and although they had not been paid to write the articles in question they had all received honoraria for other work they had done for Bayer. Professional writing support and editorial assistance was funded by Bayer HealthCare AG.

The Panel considered that Bayer Schering was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Circulation of the supplement was not limited to those who attended the meeting as it was circulated with the JBJS. Given the company's involvement and the content of the supplement, the Panel considered that the supplement was, in effect, promotional material for Xarelto. Further, the Panel noted that the supplement was not formally peer reviewed by the JBJS. The Panel considered that the material was a paid-for insert from Bayer Schering, not a supplement from the JBJS for which its editorial board would have been responsible. The back cover of the supplement stated:

'This supplement is provided free with the British Volume of JBJS. The contents have not been selected or edited by the Journal. All questions about scientific content should be addressed to the individual authors.'

The supplement was distributed with the September issue of the JBJS. Xarelto did not receive a UK marketing authorization until 1 October 2008. The Panel noted its comments above and considered that the supplement had promoted

Xarelto to UK health professionals prior to the grant of the marketing authorization. A breach was ruled as acknowledged by Bayer Schering.

The Panel did not consider that the statement 'An introduction to rivaroxaban: the first oral, once daily, direct Factor Xa inhibitor for the prevention of venous thromboembolism' implied that the product was available for prescription in September 2008 as alleged. No breach was ruled. Similarly the Panel did not consider that the claim 'Rivaroxaban offers clinicians and their patients a novel orally active anticoagulant ...' was misleading through the use of the present tense. No breach was ruled. Insomuch as the claim promoted Xarelto, however, the Panel considered that its ruling of a breach above covered this aspect.

The Panel did not consider that the statement 'Rivaroxaban will offer clinicians the opportunity to use a fixed dose, unmonitored, once-daily anticoagulant, given as a single 10mg tablet, for the prevention of VTE after major orthopaedic surgery. Importantly, unlike parental anticoagulant, Rivaroxaban will enable an easy transition from hospital to outpatient thromboprophylaxis, providing an opportunity to improve further the current standard of care in this high risk patient population' implied, as alleged, that Xarelto would work for all patients. In that regard the Panel did not consider that the statement was either misleading or exaggerated. No breach was ruled. Insomuch as the statement promoted Xarelto, the Panel considered that its ruling of a breach above covered this aspect.

The graph entitled 'Efficacy of currently available options for venous thromboembolism prophylaxis' was compiled from Geerts *et al* (2001). The data thus pre-dated the introduction of dabigatran onto the UK market. In that regard the data was not up-to-date and was misleading. Breaches were ruled.

The front cover of the supplement did not feature a statement acknowledging Bayer Schering's involvement thus a breach was ruled.

Boehringer Ingelheim was very concerned about the activities of Bayer Schering as detailed above and alleged that the company had undertaken pre-licence promotional activities. Boehringer Ingelheim was further concerned that, despite multiple discussions between the two companies regarding the need to comply with the Code, Bayer Schering had repeatedly undertaken activities in the sensitive pre-licence period which had not been through self-regulation review and approval processes according to the requirement of the Code. Taking all these activities into account Boehringer Ingelheim alleged that Bayer Schering's actions had brought the industry into disrepute in breach of Clause 2.

The Panel considered that the arrangements within Bayer Schering showed poor control. It appeared

that non UK parts of the business had little awareness of matters to be considered when conducting activities in the UK. It was the responsibility of the UK company to ensure compliance within the UK Code. A medicine had been promoted prior to the grant of its marketing authorization on more than one occasion. Taking all the circumstances into account the Panel considered that Bayer Schering had brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

Boehringer Ingelheim Limited complained that Bayer Schering Pharma had promoted its anticoagulant Xarelto (rivaroxaban) prior to the grant of its marketing authorization (Clause 3) Xarelto received its marketing authorization on 1 October 2008.

Boehringer Ingelheim marketed the anticoagulant Pradaxa (dabigatran).

Given the dates of the activities in question the Panel decided to use the provisions of the 2006 Code using the 2008 Constitution and Procedure. The clauses at issue had not changed under the two Codes but some had been renumbered.

1 Meeting of the Irish Orthopaedic Association

COMPLAINT

Boehringer Ingelheim alleged that at the Irish Orthopaedic Association meeting, Belfast, 19-20 June 2008, Bayer Schering conducted a number of activities which were in breach of the Code. In particular Bayer Schering had an exhibition stand on venous thromboembolism which stated 'Great Clinical Need for New Anticoagulants...' and then described various desirable attributes. The stand was manned by sales representatives and marketing team members. Boehringer Ingelheim was concerned that having a stand on venous thromboembolism would solicit questions on the availability of such new anticoagulants thus breaching Clause 3.1. Boehringer Ingelheim was also concerned that any such questions would be answered by promotional sales representatives, thus breaching Clause 3.1.

The stand stated 'Great Clinical Need for New Anticoagulants...' but did not mention that the new anticoagulant Pradaxa (dabigatran) with this profile was already available. Boehringer Ingelheim alleged that this was disparaging and misleading in breach of Clauses 7.2 and 8.1.

Boehringer Ingelheim noted that Bayer Schering had distributed a leaflet entitled 'Thrombosis Adviser' and a two question quiz card on deep vein thrombosis and the characteristics of an ideal anticoagulant. The quiz offered entry into a draw to win a book voucher in breach of Clause 18.2.

RESPONSE

Bayer Schering explained that Bayer Schering in the UK only knew about this meeting after the event. Bayer Schering noted that this was a problem common to many international companies.

Bayer Schering refuted the claim 'Great Clinical Need for New Anticoagulants...' was in breach of Clause 3.1. The company's presence at the meeting was entirely educational, and none of the materials on the stand could lead any doctor to believe that the information was related to a specific medicine. Indeed, as Boehringer Ingelheim stated, the exhibition panel actually listed attributes that were met by dabigatran; thus, it seemed self-evident that this exhibition panel was not specific to a Bayer Schering product, hence not in breach of Clause 3.1.

Bayer Schering acknowledged that the stand was manned by sales and marketing personnel from its affiliate in the Republic of Ireland. Had this meeting been properly certified by the UK signatories, there would of course have been no sales or marketing personnel present at the stand.

Bayer Schering refuted the allegation that the claim disparaged or misled with regard to the availability of dabigatran. The stand did not refer to an *unmet* need for a new anticoagulant, but of great clinical need for new anticoagulants. Despite the arrival of new anticoagulants for the prevention of venous thromboembolism following major orthopaedic surgery of the lower limbs, there was still undoubtedly a great clinical need for new oral anticoagulants in other therapeutic areas.

Although dabigatran (and rivaroxaban) promised to meet many of the needs for new anticoagulants, there was still a long way to go before the full extent of clinical need, across multiple therapeutic areas, was actually met. It would be seriously misleading to suggest otherwise.

Bayer Schering disagreed with the allegation that the stand was in breach of Clauses 7.2 or 8.1.

Bayer Schering contended the allegation that the distribution of the leaflet 'Thrombosis Adviser' announcing the development of a new educational website for use by both health professionals and patients, constituted a breach of Clause 18.2. Bayer Schering could not find any connection between the leaflet and Clause 18.2 and was unsure as to the exact nature of the allegation.

The quiz card was a test of the delegates' knowledge of the subject matter. It was not a promotional item and therefore not in breach of the Code. However the offer of a prize was inappropriate, in breach of Clause 18.2. However this breach should be considered in the context in which it occurred. Bayer Schering understood that its Irish colleagues limited the quiz to health professionals from the Republic of Ireland but they accepted that the process used was not totally robust.

PANEL RULING

The Panel noted that the material used at the Belfast meeting had been supplied by Bayer Schering's Irish affiliates. It was an established principle under the Code that UK companies were responsible for the activities of overseas affiliates that came within the scope of the Code. As the meeting took place in the UK, both the UK Code and the Irish Code applied. Where the two codes differed the more stringent code would apply. The exhibition stand was manned by members of the sales and marketing team from the Republic of Ireland. The Panel noted that the supplementary information to Clause 1.7, 'Applicability of Codes', made it clear that at meetings held in the UK materials and activities had to comply with the UK Code. It also stated, *inter alia*, that 'All international events, that is to say events that take place outside the responsible pharmaceutical company's home country, must be notified in advance to any relevant local subsidiary or local advice taken'.

The Panel noted that one of the exhibition panels at issue referred to VTE (venous thromboembolism) as a seriously underestimated killer. The second exhibition panel was headed 'Great Clinical Need for New Anticoagulants Providing: effective anticoagulation; low risk of bleeding; oral delivery; wide therapeutic window; fixed dosing; no monitoring; low risk of food and drug interactions and predictable pharmacology'. The Panel considered that the second exhibition panel, given the context in which it was used, ie a promotional exhibition space, in effect promoted Xarelto in June 2008 prior to the grant of its marketing authorization on 1 October 2008. The exhibition panel listed Xarelto's benefits; it would be clear to delegates that Bayer Schering had a commercial interest in an oral anticoagulant with the profile listed. A breach of Clause 3.1 was ruled.

The Panel considered that the heading to the second exhibition panel 'Great Clinical Need for New Anticoagulants Providing:' ignored the fact that Boehringer Ingelheim's new anticoagulant (Pradaxa) was already available. The heading implied that no anticoagulant was available with the properties listed which was not so. The Panel noted that Bayer Schering's submission that the unmet need referred to therapy areas other than preventing VTE following orthopaedic surgery. This was not made clear on the exhibition panel. The Panel considered that the exhibition panel was misleading and disparaging as alleged. Breaches of Clauses 7.2 and 8.1 were ruled.

The Panel noted that a leaflet distributed from the exhibition stand had asked delegates to 'Test your knowledge on VTE and enter a draw to win a book voucher from ...'. The supplementary information to Clause 18.2 of the 2006 Code stated 'The use of competitions, quizzes and suchlike, and the giving of prizes, are unacceptable methods of promotion'. The Panel considered it irrelevant that the quiz had been linked to those delegates from the Republic of

Ireland. It had taken place in the UK with UK health professionals via a promotional stand. Bayer Schering had not complied with the supplementary information to Clause 18.2 and a breach of Clause 18.2 was ruled as alleged.

2 Supplements on rivaroxaban in the Journal of Bone and Joint Surgery (JBJS) September 2008.

COMPLAINT

Boehringer Ingelheim noted that the journal was available on 4 September 2008 when rivaroxaban was unlicensed. The supplement was published in the British volume of the journal and was circulated within the UK. As it was published prior to the grant of the marketing authorization for rivaroxaban, Boehringer Ingelheim alleged a breach of Clause 3.1.

The supplement was funded by Bayer Schering as stated in the acknowledgements of each article. However, there was no clear mention of the sponsor company at the outset; Boehringer Ingelheim alleged a breach of Clause 9.10.

Boehringer Ingelheim alleged that on the cover, page 1 and page 3, the statement 'An introduction to rivaroxaban: the first oral, once-daily, direct Factor Xa inhibitor for the prevention of venous thromboembolism' was misleading in breach of Clause 7.2 as it implied that rivaroxaban was available in September 2008 for prescription.

On page 22 under the conclusion of the article, 'Rivaroxaban: venous thromboembolism risk reduction after total hip arthroplasty' the statement, 'Rivaroxaban offers clinicians and their patients a novel orally active anticoagulant for extended thromboprophylaxis in the outpatient setting' was alleged to be misleading as 'offers' was in the present tense and thus was in breach of Clauses 7.2 and 3.1.

On page 28 under conclusions of the article, 'Rivaroxaban reduces symptomatic venous thromboembolism and has a potential positive economic impact after total knee arthroplasty', the claims 'Rivaroxaban will offer clinicians the opportunity....', and the statement, 'Importantly, unlike parenteral anticoagulants, rivaroxaban will enable an easy transition...' implied that rivaroxaban would work for all patients which was alleged to be misleading and exaggerated in breach of Clause 7.2 and 7.10. In addition, Boehringer Ingelheim considered that these claims implied that rivaroxaban would definitely be available which, given that rivaroxaban was not licensed at the time of publication, was in breach of Clause 3.1.

On page 30, the graph in figure 1, 'Efficacy of currently available options for venous thromboprophylaxis' (emphasis added) did not include dabigatran which had a marketing

authorization for primary prevention of venous thromboembolism events in adults following elective total hip or knee replacement surgery and was available in the UK. Boehringer Ingelheim alleged that the graph did not reflect up-to-date evidence and was misleading in breach of Clauses 7.2 and 7.3.

RESPONSE

Bayer Schering agreed that the supplement fell within the Code and was in breach of Clause 3. The supplement should have been certified in accordance with Clause 14.

An SOP was being developed to deal with the need identified under the supplementary information to Clause 19.1, for overseas affiliates to be reminded of their obligations under the Code, in relation to their meeting activities.

Finally, the therapeutic area head, thrombosis, Bayer Healthcare AG had confirmed by email that his Global Teams and Publications Agencies had been reminded to ensure that all global materials produced in the UK and/or intended for a UK audience must be submitted to Bayer plc for certification in accordance with the relevant UK SOP.

Notwithstanding the fact that the UK signatories were unaware of the entire supplement prior to its publication, Bayer Schering nonetheless argued against two of the specific concerns raised by Boehringer Ingelheim as to the content of the supplement.

Bayer plc understood Boehringer Ingelheim concerns in relation to the statement on pages 1, 3 and 22. However its concerns were based upon the tense of the wording relating to a non-licensed product, which referred to a breach of Clause 3 and not 7.2.

Boehringer Ingelheim had suggested that the statement on page 28 implied that rivaroxaban would work for all patients and was misleading. In Bayer Schering's view, the author had discussed the potential positive impacts following arthroplasty and the ease of transition from parenteral agents. The author did not comment that the potential benefits would be experienced by any specific group, or number, of patients. Bayer Schering did not believe that the statement referred to was in breach of either Clause 7.2 or 7.10.

With regard to the allegation that the graph on page 30 of the supplement disparaged dabigatran, Bayer Schering contended that it was taken from the most up-to-date reference; although dabigatran did not feature on the graph, it was discussed in the accompanying text of the article written by the author. Bayer Schering therefore refuted any breach of Clauses 7.2 and 7.3.

In summary, Bayer plc acknowledged a breach of Clause 3 caused by the Global affiliate, which was being addressed at the highest level. The company accepted that responsibility for this lay with it under the Code. Bayer Schering refuted the other allegations.

FURTHER RESPONSE

In response to a request for further information Bayer Schering submitted that the supplement had not been distributed in the UK or to UK health professionals other than by the Journal of Bone and Joint Surgery. Bayer Schering explained that it had discussed potential educational initiatives at and arising from the 9th EFORT Congress, Nice, France, 29 May-1 June 2008 with its medical education agency.

It was agreed that educational activities to be organized around EFORT 2008 would include a satellite symposium and an educational supplement involving renowned European experts in the field, including principal investigators and steering committee members of the RECORD clinical trial programme.

The satellite symposium and supplement were produced as non-promotional, educational communications adhering to Good Publication Practice for Pharmaceutical Companies and agreed publication operating procedures established between Bayer Schering and its agency. A flow chart showing the steps followed in the publication process was provided.

The satellite session had two co-chairmen who agreed to edit the journal supplement, such editing having been previously agreed by the journal editorial board. Bayer Schering provided details of the two co-chairmen and of the other authors (the faculty) who contributed to the supplement.

The agency was responsible for contact and further discussion with the co-chairmen of the EFORT 2008 satellite symposium who were actively involved in generating the programme and proposing the faculty for the symposium; the faculty members were invited by the agency on behalf of the chairmen and Bayer Schering. All faculty members were subsequently involved in the generation of articles for the JBJS supplement.

The objective of the JBJS supplement was to provide a non-promotional, educational supplement generated by clinicians closely involved in the RECORD clinical trial programme for rivaroxaban to summarize clinical data that had not been presented to European orthopaedic surgeons, but had been presented previously at haematology congresses in the US in December 2007. Important new data, which was to be published in the New England Journal of Medicine and The Lancet, were to be incorporated to provide context for surgeons for these clinically important data. These objectives

were considered by the co-editors of the supplement to be an important educational requirement for surgeons attending the congress and for a wider audience reading orthopaedic journals.

The involvement of Bayer Schering in initiating the process was therefore to brief the agency on the broad educational objectives for the satellite meeting and the JBJS supplement.

Author selection for the supplement was based on the faculty speakers who participated at the Bayer Schering sponsored symposium entitled 'Improving patient outcomes after major orthopaedic surgery', which took place on Friday, 30 May 2008 during the 9th EFORT congress in Nice, France. The initial choice of faculty was based on their relevant clinical expertise and involvement in the RECORD clinical trial programme as either principal investigators or steering committee members, and was agreed in discussions between the agency, the co-chairmen and Bayer Schering. These discussions resulted in the agency being asked to invite the agreed faculty. The invitation to participate in both the satellite session and the subsequent supplement was issued by the agency on behalf of both the chairmen and Bayer Schering.

The co-chairmen of the symposium (and co-editors of the supplement) wrote the short introductory and concluding articles for the supplement entitled 'An introduction to rivaroxaban: the first oral, once-daily, direct Factor Xa inhibitor for the prevention of venous thromboembolism' and 'Anticoagulants after orthopaedic surgery: where are we now?' respectively. The other four articles included in the main body of the supplement were written by the four faculty members; one article was written by two other co-authors.

All faculty members of the EFORT 2008 satellite symposium were lead authors in the JBJS supplement. While faculty members were reimbursed for travel costs, accommodation, congress registration at EFORT and received an honorarium for their involvement with the symposium, no payment was made relating to development of articles within the subsequent JBJS supplement.

The objective was to provide the proceedings of the educational symposium at EFORT 2008 in the form of a supplement. All authors considered providing data on rivaroxaban was essential to ensure fair scientific balance, and was important in the education of their peers. All data included in the articles were referenced to peer reviewed publications and reflected the views of the authors.

Following author agreement to contribute articles to the supplement, the agency obtained author briefs from the faculty for the focus of the manuscripts for each article. Briefs from authors were taken by telephone and publications were progressed by the agency in line with this direction. Full author input

was sought and provided at each subsequent stage as per the publication process document provided.

The JBJS did not conduct a formal peer-review procedure for supplements. In order to ensure fair balance and accurate presentation, it was considered important to include a review process for the supplement. The agency offered suggestions on a potential peer review process and, in line with this, the JBJS academic editor accepted the proposal that the co-chairmen of the symposium peer review and guest edit the supplement. Therefore, all draft manuscripts were submitted to the co-chairmen (co-editors of the supplement) for review, as agreed with JBJS.

Before final author review and approval of articles, draft manuscripts were submitted to Bayer Schering's global publication review team, to check the accuracy and validity of any rivaroxaban scientific and clinical trial data to be featured in the supplement. In accordance with Good Publication Practice for Pharmaceutical Companies, comments were provided directly to the authors for their consideration whereupon the authors made their final amendments, commenting where relevant, and gave their final approval of the submission drafts. The comments from Bayer Schering were marked up by the agency and forwarded to the authors for their review and decision on whether the comments be implemented. All authors had ultimate editorial control of their articles.

All authors were involved fully in directing the writing of their individual manuscript, from initial specification to final piece. This involved review and input of interim drafts, to final comment and approval of each submitted version. Professional writing support and editorial assistance was provided by the agency to authors at their request and under their direction, in the preparation of their manuscripts. This support was funded by Bayer HealthCare AG (part of the Bayer AG Group) and, in accordance with accepted Good Publication Practice, was fully acknowledged by the authors in their articles along with additional disclosure statements.

PANEL RULING

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

promotional purposes.

The Panel noted that the objective of the material in question, 'Improving Patient Outcomes After Major Orthopaedic Surgery', was to provide the proceedings of a symposium, sponsored by Bayer Schering at an international meeting, in the form of a journal supplement. The Panel considered that it would not always be possible to achieve this and comply with the requirements of the Code. Within the context of an international conference, attended by thought leaders, investigators and the like, it was possible for pharmaceutical companies to hold symposia about unlicensed products or indications as long as such activities were not otherwise promotional. The Code did not prohibit the legitimate exchange of medical and scientific information during the development of a medicine. The unsolicited distribution of symposia proceedings by a pharmaceutical company to health professionals who had not attended the meeting was not acceptable if the material promoted unlicensed medicines or did not otherwise comply with the Code.

The Panel noted that the supplement had been initiated by Bayer Schering and its agency. The co-editors and first authors were those who had taken part in the company-sponsored symposium at EFORT 2008 and although they had not been paid to write the articles in question they had all received honoraria for other work they had done for Bayer. Professional writing support and editorial assistance was funded by Bayer HealthCare AG.

The Panel considered that Bayer Schering was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Circulation of the supplement was not limited to those who attended the meeting as it was circulated with the JBJS. Given the company's involvement and the content of the supplement, the Panel considered that the supplement was, in effect, promotional material for Xarelto. Further, the Panel noted that the supplement was not formally peer reviewed by the JBJS. The Panel considered that the material was a paid-for insert from Bayer Schering, not a supplement from the JBJS for which its editorial board would have been responsible. The back cover of the supplement stated

'This supplement is provided free with the British Volume of JBJS. The contents have not been selected or edited by the Journal. All questions about scientific content should be addressed to the individual authors'.

The supplement was distributed with the September issue of the JBJS. Xarelto did not receive a UK marketing authorization until 1 October 2008. The Panel noted its comments above and considered that the supplement had promoted Xarelto to UK health professionals prior to the grant

of the marketing authorization. A breach of Clause 3.1 was ruled as acknowledged by Bayer Schering.

The Panel did not consider that the statement 'An introduction to rivaroxaban: the first oral, once daily, direct Factor Xa inhibitor for the prevention of venous thromboembolism' implied that the product was available for prescription in September 2008 as alleged. No breach of Clause 7.2 was ruled. Similarly the Panel did not consider that the claim 'Rivaroxaban offers clinicians and their patients a novel orally active anticoagulant ...' was misleading through the use of the present tense. No breach of Clause 7.2 was ruled. Insomuch as the claim promoted Xarelto, however, the Panel considered that its ruling of a breach of Clause 3.1 above covered this aspect.

The Panel did not consider that the statement 'Rivaroxaban will offer clinicians the opportunity to use a fixed dose, unmonitored, once-daily anticoagulant, given as a single 10mg tablet, for the prevention of VTE after major orthopaedic surgery. Importantly, unlike parental anticoagulant, Rivaroxaban will enable an easy transition from hospital to outpatient thromboprophylaxis, providing an opportunity to improve further the current standard of care in this high risk patient population' implied, as alleged, that Xarelto would work for all patients. In that regard the Panel did not consider that the statement was either misleading or exaggerated. No breach of Clauses 7.2 and 7.10 was ruled. Insomuch as the statement promoted Xarelto, the Panel considered that its ruling of a breach of Clause 3.1 above covered this aspect.

Page 30 of the supplement included a graph entitled 'Efficacy of currently available options for venous thromboembolism prophylaxis' the data for which was compiled from Geerts *et al* (2001). The data thus pre-dated the introduction of dabigatran onto the UK market. In that regard the data was not up-to-date and was misleading. Breaches of Clauses 7.2 and 7.3 were ruled.

Clause 9.10 required that material relating to medicines and their uses, whether promotional in nature or not, which was sponsored by a pharmaceutical company, must clearly indicate that it has been sponsored by that company. The front cover of the supplement did not feature a statement acknowledging Bayer Schering's involvement. Disclosures at the end of each article as to Bayer Schering's relationship with the author were not sufficient in this regard. A breach of Clause 9.10 was ruled.

3 Alleged breach of Clause 2

COMPLAINT

Boehringer Ingelheim was very concerned about the activities of Bayer Schering as detailed above and alleged that the company had undertaken pre-licence promotional activities. Boehringer

Ingelheim was further concerned that, despite multiple discussions between the two companies regarding the need to comply with the Code, Bayer Schering had repeatedly undertaken activities in the sensitive pre-licence period which had not been through self-regulation review and approval processes according to the requirement of the Code. Taking all these activities into account Boehringer Ingelheim alleged that Bayer Schering's actions had brought the industry into disrepute in breach of Clause 2.

RESPONSE

Bayer Schering strongly denied that its UK certification process was flawed. The company strongly refuted all of the claims made by Boehringer Ingelheim in relation to the Anticoagulation Congress in Birmingham.

Bayer Schering agreed that there were two related breaches of Clause 14 relating to the Irish Orthopaedic Association meeting and the JBJS supplement (which included other associated breaches). Having occurred very close together, Bayer Schering regarded these events as manifestations of the same international problem. This issue was already being addressed when both infractions occurred; in a large multi-national

organisation, a certain amount of time was required for the finalisation and implementation of new processes. As explained above, this matter had been taken very seriously, and was actively being addressed at the highest level. Bayer Schering did not consider that its actions were such as to breach Clause 2.

PANEL RULING

The Panel considered that the arrangements within Bayer Schering showed poor control. It appeared that non UK parts of the business had little awareness of matters to be considered when conducting activities in the UK. It was the responsibility of the UK company to ensure compliance within the UK Code. A medicine had been promoted prior to the grant of its marketing authorization on more than one occasion. Taking all the circumstances into account the Panel considered that Bayer Schering had brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

Complaint received	9 October 2008
Case completed	23 December 2008

NURSE v SYNER-MED

Ferinject detail aid

A nurse alleged that the revised edition of a Ferinject (ferric carboxymaltose) detail aid entitled 'The next generation of intravenous iron' issued by Syner-Med was inaccurate.

Page 1 of the detail aid, headed 'What is required of the next generation intravenous iron?', listed five features, the second of which was 'Single dose delivery'. The list was followed by a chart detailing administration details of, *inter alia*, iv iron dextran (Vitaline Pharma UK's product CosmoFer). It was stated that [CosmoFer] could be given in a 200mg bolus which was not true. It took 35 minutes to give 200mg iron dextran. It was not accurate to state that the 1000mg infusion time for iv iron dextran was 4-6 hours when a patient with a body weight of 75kg could receive 1500mg of iron dextran, a much larger dose, as a total dose infusion over four hours. Page 1 also referred to single dose delivery. This was misleading as a patient had to weigh over 67kg to receive 1000mg of Ferinject.

The detailed response from Syner-Med is set out below.

The Panel noted that the CosmoFer summary of product characteristics (SPC) required a test dose of 25mg to be administered before the first dose could be given to a new patient. If no adverse reactions were seen after 60 minutes, the remaining dose could be given. The dose and dosage schedule must be individually estimated for each patient. The dosage schedule normally recommended was 100-200mg iron corresponding to 2-4ml two or three times a week depending on the haemoglobin level. In certain circumstances CosmoFer could be administered as a total dose infusion up to a total replacement dose corresponding to 20mg iron/kg body weight. Subsequent doses depended on the method of administration. If given via an intravenous drip 100-200mg of iron could be diluted in 100ml of normal saline or 5% glucose solution. On each occasion the first 25mg should be infused over a period of 15 minutes. If there were no adverse reactions the remaining portion should be given at a rate of not more than 100ml in 30 minutes. If CosmoFer was being given as an iv injection 25mg of iron should be injected slowly over a period of 1 to 2 minutes. If no adverse reactions occurred within 15 minutes the remaining portion could be given. The product could also be given as a total dose infusion up to 20mg/kg body weight iv over 4-6 hours. The first 25mg of iron to be infused over 15 minutes. The SPC stated that this method of administration should be restricted to hospital use only. The SPC stated that the iv drip infusion was

the preferred route of administration. However it could be administered as undiluted solution intramuscularly.

The Panel did not consider that the chart detailing, *inter alia*, the administration of CosmoFer was sufficiently clear as to the route of administration and dosing schedule being referred to. There was no mention that each patient's dose had to be calculated individually according to haemoglobin levels. It appeared that for CosmoFer there was a choice of two doses; 200mg or 1000mg. It appeared that the 200mg bolus dose could be administered over 10 minutes which was not so; there was no indication that the total injection time was comprised of the time taken to administer the test dose plus the time needed to administer the rest of the dose. The Panel considered that the chart was too simple given the complex dosing instructions for CosmoFer. The chart was misleading in this regard and a breach of the Code was ruled.

The Panel did not consider that it was incorrect to state that the infusion time for a 1000mg dose of CosmoFer would be 4-6 hours. It would have been helpful to state that this was not a fixed dose but was dependent upon a patient's body weight and haemoglobin level. Nonetheless, if a dose of 1000mg was required it could be infused over 4-6 hours. The Panel thus considered that the material was not misleading as alleged and no breach was ruled.

With regard to the statement 'Single dose delivery' the Panel noted that this was one response to the question 'What is required of the next generation intravenous iron?'. The Panel noted that the front cover of the brochure was headed 'Ferinject' followed by 'The next generation intravenous iron'. Page 3, facing page 2, was headed 'Ferinject the next generation intravenous iron' and thus the features listed on page 1 would be read as applying to Ferinject. According to its SPC Ferinject could be administered as a maximum single dose of 20ml of Ferinject (1000mg of iron) but not exceeding 0.3ml of Ferinject (15mg of iron) per kg body weight per week. The Panel noted that the administration of Ferinject was not straightforward but page 1 implied that it was. The list featured on page 1 was repeated on page 10 but with a comment about Ferinject next to each feature. On page 10 the claim 'Single dose delivery' was followed by 'Up to 1000mg* but not exceeding 15mg/kg/wk'. The asterisked footnote stated that the iron deficit should be calculated (see SPC) and that a single dose should not exceed 15mg/kg/wk. The Panel considered that page 1 was misleading as alleged and a breach of the Code was ruled.

A nurse complained about the revised edition of a Ferinject (ferric carboxymaltose) detail aid entitled 'The next generation of intravenous iron' (ref F17) issued by Syner-Med (Pharmaceutical Products) Limited.

Page 1 of the detail aid, headed 'What is required of the next generation intravenous iron?', listed five features, the second of which was 'Single dose delivery'. The list was followed by a chart detailing administration details of, *inter alia*, iv iron (iii) hydroxide dextran complex (Vitaline Pharma UK's product CosmoFer).

The complainant had complained previously about the promotion of Ferinject (Cases AUTH/2143/7/08 and AUTH/2144/7/08).

COMPLAINT

The complainant alleged that the updated version of the detail aid was unfortunately still inaccurate.

Page 1 stated that iron dextran [CosmoFer] could be given in a 200mg bolus which was not true. It took 35 minutes to give 200mg iron dextran. It was not accurate to state that the 1000mg infusion time for iv iron dextran was 4-6 hours when a patient with a body weight of 75kg could receive 1500mg of iron dextran, a much larger dose, as a total dose infusion over four hours.

Page 1 also referred to single dose delivery. This was misleading as a patient had to weigh over 67kg to receive 1000mg of Ferinject.

When writing to Syner-Med, the Authority asked it to respond in relation to Clause 7.2 of the Code which was the same in the 2008 Code as the 2006 Code.

RESPONSE

Syner-Med explained that iron dextran was licensed to be administered intramuscularly, intravenously or via the venous limb of a dialyser. The intravenous route permitted the product to be administered either as an infusion or injection. The definition of a bolus injection was (medical online dictionary) 'The injection of a drug (or drugs) in a high quantity (called a bolus) at once, the opposite of gradual administration (as in intravenous infusion)'. The CosmoFer summary of product characteristics (SPC) stated 100 – 200mg iron (2-4mls) by slow intravenous injection. The statement was thus correct and in line with the CosmoFer SPC.

The complainant was correct that it took 35 minutes to give 200mg iron dextran. However the complainant had not noted that the information on page 1 broke down the administration time of iron dextran into the time it took to administer a test dose and the time it took to administer the remaining portion of the dose.

Syner-Med submitted that the time that it might take to administer 1000mg of iron dextran was correctly stated in the detail aid. There was no attempt to provide specific prescribing information regarding the minimum or maximum dosage of iron dextran and no attempt to provide specific prescribing information for individual patients. The statement that the 1000mg infusion time was 4-6 hours was correct and in line with the CosmoFer SPC.

Syner-Med noted that the statement 'Single dose delivery' appeared under the question 'What is required of the next generation intravenous iron?' and referred to potential product characteristics which health professionals might find beneficial when treating patients with parenteral iron. There was no reference on this page to the prescribing of Ferinject. The company did not believe that the information or statements were misleading.

PANEL RULING

The Panel noted that the CosmoFer SPC required a test dose of 25mg to be administered before the first dose could be given to a new patient. If no adverse reactions were seen after 60 minutes, the remaining dose could be given. The dose and dosage schedule must be individually estimated for each patient. The dosage schedule normally recommended was 100-200mg iron corresponding to 2-4ml two or three times a week depending on the haemoglobin level. In certain circumstances CosmoFer could be administered as a total dose infusion up to a total replacement dose corresponding to 20mg iron/kg body weight. Subsequent doses depended on the method of administration. If given via an intravenous drip 100-200mg of iron could be diluted in 100ml of normal saline or 5% glucose solution. On each occasion the first 25mg should be infused over a period of 15 minutes. If there were no adverse reactions the remaining portion should be given at a rate of not more than 100ml in 30 minutes. If CosmoFer was being given as an iv injection 25mg of iron should be injected slowly over a period of 1 to 2 minutes. If no adverse reactions occurred within 15 minutes the remaining portion could be given. The product could also be given as a total dose infusion up to 20mg/kg body weight iv over 4-6 hours. The first 25mg of iron to be infused over 15 minutes. The SPC stated that this method of administration should be restricted to hospital use only. The SPC stated that the iv drip infusion was the preferred route of administration. However it could be administered as undiluted solution intramuscularly.

The Panel did not consider that the chart on page 2 of the detail aid, detailing, *inter alia*, the administration of CosmoFer was sufficiently clear as to the route of administration and dosing schedule being referred to. There was no mention that each patient's dose had to be calculated individually according to haemoglobin levels. It appeared that for CosmoFer there was a choice of two doses;

200mg or 1000mg. It appeared that the 200mg bolus dose could be administered over 10 minutes which was not so; there was no indication that the total injection time was comprised of the time taken to administer the test dose plus the time needed to administer the rest of the dose. The Panel considered that the chart was too simple given the complex dosing instructions for CosmoFer. The chart was misleading in this regard and a breach of Clause 7.2 was ruled.

The Panel did not consider that it was incorrect to state that the infusion time for a 1000mg dose of CosmoFer would be 4-6 hours. It would have been helpful to state that this was not a fixed dose but was dependent upon a patient's body weight and haemoglobin level. Nonetheless, if a dose of 1000mg was required it could be infused over 4-6 hours. The Panel thus considered that the material was not misleading as alleged and no breach of Clause 7.2 was ruled.

With regard to the statement 'Single dose delivery' the Panel noted that this was one response to the question 'What is required of the next generation intravenous iron?'. The Panel noted that the front

cover of the brochure was headed 'Ferinjected' followed by 'The next generation intravenous iron'. Page 3, facing page 2, was headed 'Ferinjected the next generation intravenous iron' and thus the features listed on page 1 would be read as applying to Ferinjected. According to its SPC Ferinjected could be administered as a maximum single dose of 20ml of Ferinjected (1000mg of iron) but not exceeding 0.3ml of Ferinjected (15mg of iron) per kg body weight per week. The Panel noted that the administration of Ferinjected was not straightforward but page 1 implied that it was. The list featured on page 1 was repeated on page 10 but with a comment about Ferinjected next to each feature. On page 10 the claim 'Single dose delivery' was followed by 'Up to 1000mg* but not exceeding 15mg/kg/wk'. The asterisked footnote stated that the iron deficit should be calculated (see SPC) and that a single dose should not exceed 15mg/kg/wk. The Panel considered that page 1 was misleading as alleged and a breach of Clause 7.2 was ruled.

Complaint received 10 October 2008

Case completed 25 November 2008

ANONYMOUS v MERCK SERONO

Alleged inappropriate hospitality

An anonymous, uncontactable complainant alleged that Merck Serono had breached the Code at a recent meeting for fertility nurses.

The complainant alleged that Merck Serono had provided entertainment at the meeting in the form of an after dinner speaker at the gala dinner. The complainant considered that this was outside the spirit of the Code and even though the speaker was medically trained his remit was one of entertainment rather than being educational.

The complainant was further concerned that the vast number of delegates that were fully sponsored by Merck Serono were from centres which exclusively used its fertility portfolio and that there were only a handful of attendees that were from non-Merck Serono centres that were self-payers.

The complainant also suspected that the sales team was being asked to sell Pergoveris outside its licensed indication.

The detailed response from Merck Serono is given below.

The Panel noted that the meeting was an annual conference for nursing professionals and paramedical staff involved in fertility. The meeting was sponsored by Merck Serono and lasted two and a half days. The Panel had not been provided with a copy of the original brief but a document showed that the speaker had been asked to present a thought provoking examination of the NHS in a light-hearted manner with particular attention to the changing role of the nurse. He was asked to engage the audience on: access to NHS funding; the changing role of the nurse in fertility treatment and the role of the regulator. To finish with a question and answer session the speaker was told that his talk would come at the end of a long day of educational training. Merck Serono submitted that the speaker had spoken to delegates to understand their issues and tailor his talk accordingly.

The Panel considered that given his experience as a media doctor, the presentation would have been amusing despite the subject matter being educational and relevant. He had not been given a remit to provide entertainment. In that regard and in the context of the educational content of the entire meeting the Panel did not consider that the after dinner speech had been inappropriate as alleged. No breach of the Code was ruled.

The Panel noted that the complainant further alleged that Merck Serono had mainly sponsored delegates from centres that exclusively used its

fertility products. The Panel considered that there was no evidence to show that product usage had influenced delegate sponsorship. No breach of the Code was ruled.

The statements in the training material and the promotional material were consistent with the indication as stated in the summary of product characteristics. The Panel considered that there was no evidence to show the sales force had been asked to sell Pergoveris outwith its licensed indication as alleged. No breach of the Code was ruled.

The Panel considered that, given its rulings above, there could be no breach of Clause 2.

An anonymous, uncontactable complainant alleged that Merck Serono had breached the Code at a recent Insights meeting for fertility nurses held on 1-3 October in Brighton.

COMPLAINT

The complainant alleged that Merck Serono had provided entertainment at the meeting in the form of an after dinner speaker at the gala dinner held on 2 October. The complainant considered that this was outside the spirit of the Code and even though the speaker was medically trained his remit was one of entertainment rather than being educational.

The complainant was further concerned that the vast number of delegates that were fully sponsored by Merck Serono were from centres which exclusively used its fertility portfolio and that there were only a handful of attendees that were from non-Merck Serono centres that were self-payers.

The complainant also suspected that the sales team was being asked to sell Pergoveris outside of its licensed indication.

When writing to Merck Serono the Authority asked it to respond in relation to Clauses 2, 3.1, 15.9 and 19.1 of the Code. The matter was considered under the 2006 Code using the 2008 Constitution and Procedure.

RESPONSE

Merck Serono explained that the INSIGHTS annual conference was in its 24th year and in that time had become one of the most important and highly valued educational vehicles for nurses specialised in the treatment of infertility. Merck Serono had sponsored this conference since its inception in

1984. Insights 2008 was held from 1-3 October and was attended by 134 fertility specialist nurses (124 delegates plus 10 steering committee members). The 3 day programme was developed by the Insights steering committee which was principally made up of members of the senior infertility nurse group. A list of clinics represented on the steering committee was provided. The steering committee planned Insights 2008 using feedback from the 2007 conference as well as incorporating hot topics reflecting current nursing needs. The focus of the meeting was, as always, the nurse educational content. The aim was to provide a stimulating programme along with a forum for useful debate as well as time for networking with colleagues from around the country. Over the 3 days, more than 13 hours of education was provided by 24 expert speakers. A copy of the agenda and invitation to the meeting was provided.

On the evening of the 2 October after the final conference dinner, the speaker gave a talk to the delegates on the current state of the health service with particular reference to the changing role of the nurse. The speaker was a practicing GP with relevant experience in sexual health. Merck Serono disputed the allegation that the remit was purely one of entertainment. Whilst the talk was delivered in an entertaining manner, as was often the case with accomplished speakers, the content was educational and relevant. A copy of the brief was provided. In the absence of a full transcript Merck Serono noted some of the topics covered in the 30-40 minute talk:

- His experience, as a GP, of the struggles faced by infertile couples seeking access to NHS funding.
- The role of the regulator in medicine including the role of the Human Fertilisation and Embryo Authority within the fertility arena
- The changing role of both doctors and nurses in medical practice
- Questions and answers.

In addition, before his presentation, the speaker talked to delegates to better understand their issues and tailor his talk accordingly. Throughout his talk he encouraged the delegates to share their experiences on the topics covered.

In summary, Merck Serono submitted that an appropriate speaker was used and that the topics covered were relevant and educational to the delegates.

Following the conference, delegates were anonymously surveyed to ascertain their feedback on the quality of the education provided and to what extent the conference had been successful in fulfilling their personal educational objectives. 98% of delegates rated the quality of the education excellent or good with 2% rating it as satisfactory with nobody rating it as poor. 98% of delegates considered the conference had been very successful or mostly successful in fulfilling their personal educational objectives. 2% considered it slightly

successful and nobody rated it as not successful. A copy of this feedback report was provided. As well as rating the meeting, the delegates were also able to make additional comments on the feedback form. No negative feedback on the content or delivery of the presentation at issue was received.

The cost of the dinner on 2 October was negotiated as part of a 24 hour delegate rate of £162 per person. This included accommodation, 3 course dinner (menu provided), afternoon tea, coffee and biscuits, buffet lunch, morning tea, coffee and pastries, and breakfast. This cost also included the hire of the main conference room.

Splitting out the cost of the dinner was difficult as it was included in the 24 hour delegate rate. However the bed and breakfast rate (for those staying only one night) was £109 and the day delegate rate (to include lunch, room hire, teas, coffee, biscuits in morning and afternoon) was £48 giving a total of £157. As the 24 hour delegate rate was £162 (to include all of the above plus dinner) the cost of the dinner per person was £5. Each delegate was provided with half a bottle of house wine. The cost of the food and wine at the conference dinner was £14.25 per person.

In addition to the food and wine provided on the evening of the 2 October, Merck Serono noted that the hotel provided a glass of complementary house sparkling wine prior to dinner by way of apology to the delegates for disappointment caused following an error made on the previous evening. This service was not paid for, or requested by Merck Serono. An explanatory email from the hotel was provided.

With regard to the sponsorship of delegates Merck Serono submitted that 124 delegates attended at least part of the conference. Seventy nine delegates (64%) were fully sponsored by Merck Serono to include:

- Full conference registration.
- Accommodation and breakfast at the conference hotel on the 1 and 2 October
- Lunch, tea and coffee throughout the conference
- Dinner on 1 and 2 October.

Members of the steering committee were in addition offered full sponsorship to attend the meeting. Ten members of the steering committee attended.

The remaining 45 delegates (36%) were offered a subsidised full conference package for £390. It included:

- Full conference registration.
- Accommodation and breakfast at the conference hotel on the 1 and 2 October
- Lunch, tea and coffee throughout the conference
- Dinner on the 1 and 2 October.

A subsidised daily delegate rate was also available for £60 per day that included:

- Conference registration fee for the chosen day(s)
- Lunch, tea and coffee for chosen day(s).

One hundred and twenty four delegates, 10 steering committee members, 12 members of Merck Serono staff and 3 members from the event management company attended. The cost per head was therefore £666, substantially more than the £390 per head which the self-funding delegates paid to attend.

The number of Merck Serono fully sponsored delegates was limited to 80. Due to the high value placed on Insights by fertility specialist nurses, demand for fully sponsored places always outstripped availability. In order to be as equitable as possible, in the first instance Merck Serono aimed to offer fully sponsored places to clinics that did not receive them the previous year for whatever reason. If fully sponsored places still remained, they were offered on a first come first served basis. Places were offered to clinics not to individuals. Clinics decided who they would like to attend.

Registration for subsidised self-funders was open to any fertility specialist nurse through the Insights website from July 2008. Pages of the website were provided. In 2008 the number of subsidised self-funders was limited to 50 as the conference room booked had a capacity of 150.

In response to the allegation 'that the vast number of delegates that were fully sponsored by Merck Serono were from centres exclusively using its fertility portfolio', Merck Serono noted the following points:

- The meeting was aimed at and attended by fertility specialist nurses. Fertility nurses were not able to prescribe medicines used in the treatment of infertility
- Merck Serono knew of no fertility clinic in the UK that exclusively used one company's products. It was important to ensure that clinics had access to a range of different medicines so they could offer choice to their patients.

Of course, particular clinics had a preference for particular products. It was however impossible for Merck Serono to know with any degree of certainty what this preference was at any particular time. Clinics did not make their product usage data publicly or commercially available.

In the absence of this data however, Merck Serono had estimated the current level of usage of its fertility products in the clinics of the fully sponsored delegates and in those of the subsidised self-funders. Details were provided

In summary, all delegates were either fully sponsored or substantially subsidised to attend Insights 2008, over one third falling in the latter category. Merck Serono submitted that it had made every effort to ensure that full sponsorship was offered in as equitable a manner as possible and that the estimated Merck Serono product usage profile of fully sponsored delegates did not differ significantly from that of the subsidised self-funders.

With regard to the third allegation centred on the promotion of Pergoveris. Merck Serono stated that it was very difficult to respond when the complainant has not provided any evidence for their suspicion. The company refuted the allegation.

Pergoveris received its marketing authorization in June 2007 and was launched in the UK in October 2007. The Merck Serono sales team was trained on its use in September 2007. In April 2008 the sales team had this training refreshed using the same training slides. Copies of the slides were provided. At both of these training sessions the licensed indication for the product was clearly stated.

Merck Serono provided copies of the current Pergoveris promotional literature and summary of product characteristics (SPC) and stated that these materials were available at the conference.

PANEL RULING

The Panel noted that the Insights 2008 meeting was an annual conference for nursing professionals and paramedical staff involved in fertility. The meeting was sponsored by Merck Serono and lasted two and a half days (from 10am, 1 October to 1pm, 3 October). The complainant alleged that the after dinner speaker on 2 October (the speaker) had provided entertainment rather than education. The Panel had not been provided with a copy of the original brief given to the speaker but a document from the event organising company showed that he had been asked to present a thought provoking examination of the NHS in a light-hearted manner with particular attention to the changing role of the nurse. He was asked to engage the audience on: access to NHS funding; the changing role of the nurse in fertility treatment and the role of the regulator. The speaker was asked to finish off the talk with a question and answer session and told that his talk would come at the end of a long day of educational training. The Panel noted Merck Serono's submission that the speaker had spoken to delegates to understand their issues and tailor his talk accordingly.

The Panel considered that given his experience as a media doctor, the presentation would have been amusing despite the subject matter being educational and relevant. He had not been given a remit to provide entertainment. In that regard and in the context of the educational content of the entire meeting the Panel did not consider that the after dinner speech had been inappropriate as alleged. No breach of Clause 19.1 was ruled.

The Panel noted that the complainant further alleged that Merck Serono had mainly sponsored delegates from centres that exclusively used its fertility products. The complainant had not produced any evidence in this regard. Merck Serono had stated that it was impossible for it to know exactly which products were used in particular clinics at any one time. The company had submitted

that its sponsorship of delegates did not show preference to those clinics that favoured its products although such data could only be based on estimates. The Panel considered that there was no evidence to show that product usage had influenced delegate sponsorship. No breach of Clause 19.1 was ruled.

The Panel noted the complainant also suspected that the sales team was being asked to sell Pergoveris outside its licensed indication. No further details were given. Merck Serono had provided copies of the representatives' training slides and a copy of a current piece of promotional literature. The training slides clearly stated that the licensed indication was for the stimulation of follicular development in women with severe LH (luteinising hormone) and FSH (follicle stimulating hormone) – in clinical trials these patients were

defined by an endogenous serum LH level < 1.2 IU/L. The promotional material stated that Pergovis was indicated for women with severe LH and FSH deficiency (defined as endogenous serum LH < 1.2IU/L). The statements in the training material and the promotional material were consistent with the indication as stated in the SPC. The Panel considered that there was no evidence to show the sales force had been asked to sell Pergoveris outwith its licensed indication as alleged. No breach of Clauses 3.1 and 15.9 was ruled.

The Panel considered that, given its rulings above, there could be no breach of Clause 2 of the Code.

Complaint received 13 October 2008

Case completed 10 November 2008

ANONYMOUS GENERAL PRACTITIONER v PROSTRAKAN

Osteoporosis audit service

An anonymous, non-contactable, general practitioner complained about an osteoporosis audit service offered by ProStrakan. ProStrakan marketed Adcal-D₃, a calcium and vitamin D₃ supplement.

The complainant explained that the audit service was offered as an Osteoporosis Project to enable better care of patients with osteoporosis. His practice had used these types of services in the past, they had always focussed on patient care, whole disease areas and not on prioritising the prescribing of one particular product. In this instance however he found himself in a very uncomfortable position with an expectation that he would prescribe only one product at the end – ProStrakan's.

The representative from ProStrakan first highlighted the service to him and suggested that it was approved by the local primary care trust (PCT) although the complainant was unable to verify this. The service was being delivered by an independent company – which, it was claimed, would complete the service in the practice without any undue interference from ProStrakan. The complainant signed the contract which stated that 'The service is not linked to the use of any particular product'. The protocol and guidelines referenced were nationally recognised criteria and all seemed very professional.

A pharmacist then completed a number of audits on the practice database to identify at-risk cohorts of patients. The complainant then had a discussion with the pharmacist which had prompted this complaint. After the conversation with the pharmacist the complainant was left with the following suggestions which made him feel uncomfortable:

- 1 Although the audits claimed to identify at-risk osteoporosis patients, they only looked to identify patients for Adcal-D₃. When the complainant asked if they could also consider bisphosphonates he was told that the company was not willing to fund an area where it did not have products.
- 2 The pharmacist indicated that the expectation was that Adcal-D₃ would be prescribed and not any alternative product – as the review was being sponsored by ProStrakan.
- 3 The complainant was informed that patient records had already been updated with the recommendations according to the protocol previously agreed with the ProStrakan representative. The complainant was told that he had to ensure that he signed to 'make it official'.

- 4 The complainant felt very uncomfortable but compelled to agree with the pharmacist as changes to patient records had already taken place – and the changes recommended did not compromise patient care.
- 5 The only changes suggested were the addition of Adcal-D₃ – in all patients.
- 6 When the complainant requested that the additional prescription medicine should be explained to patients personally by the pharmacist in either clinics or by telephone, he was told that there was not enough funding to spend the additional time and that the practice had to send letters to patients and handle patient queries. The template letter provided did not refer to the service provider or to ProStrakan's support of the service.

This experience had severely dented the complainant's confidence in working with the pharmaceutical industry on these types of services, even with previously positive experiences. The explanation from ProStrakan regarding the service was clearly a very different brief to that given to the pharmacist who carried out the service.

The complainant hoped that the Authority would be able to investigate and reassure health professionals working with pharmaceutical industry partners that services were based solely on improving patient care and not, as the complainant felt in this instance, to purely increase the prescription of a specific medicine.

The detailed responses from ProStrakan are given below.

The Panel noted that as the complainant was anonymous and non-contactable it was not possible for ProStrakan to respond in detail to the specific points raised about the audit.

The Panel considered that much would depend on the practice which had control of the process. The protocol required signatures before any audit could start. The practice could decide what action to take. It was vital that the pharmacists conducting the audit on behalf of ProStrakan followed the protocol as well as complying with their professional code. There was no evidence that they had not done so.

The Panel did not consider that the service was an osteoporosis audit service as stated by the complainant and some of the documentation. For example the document describing the service to prescribers was entitled 'Calcium and Vitamin D Supplementation Clinical Review Protocol'. The practice authorization form referred to a 'calcium

and vitamin D₃ Deficiency Clinical Review'. It was confusing as the representatives' briefing note referred to an 'Osteoporosis Review' and a chart summarising the operation of the service was headed 'Osteoporosis Therapy Review Service'. The Pharmacist Briefing Document also referred to the service as an 'Osteoporosis Therapy Review Service'. The Panel was concerned that the documentation misnamed the service. It was likely that the representative had referred to an osteoporosis review service and this had contributed to the confusion.

The Panel noted that the protocol listed calcium and vitamin D₃ supplements in alphabetical order and gave details of their formulation and strength. Doctors were to indicate their preferred product and to decide whether an initial prescription should be raised and sent to patients. The first two products identified were Adcal-D₃ and Adcal-D₃ Dissolve respectively. The Panel noted that the formulation column listed 'Chewable Tab Lemon Tutti Frutti' for Adcal-D₃. The only details for all the other products, including Adcal-D₃ Dissolve, were 'Effervescent Tab', 'Chewable Tab' or 'Sachet' as appropriate. The Panel noted ProStrakan's submission that the two flavours of Adcal-D₃ chewable tablets had been listed because such information was part of the registered name. Conversely, all of the other products were only available in one flavour and so no flavour was stated for these. This however, was not clear to the reader. Further, the Panel considered that ProStrakan's submission about the flavours of Adcal-D₃ and the registered product names was misleading. From the summaries of product characteristics (SPCs) provided by ProStrakan, the tutti-frutti tablets were called 'Adcal-D₃ Chewable tablets' and the lemon flavoured tablets were called 'Adcal-D₃ Lemon Chewable tablets'.

The Panel noted that if there was evidence to show that the pharmacist had indicated that the expectation was that Adcal-D₃ would be prescribed then this would have been unacceptable. Similarly it would be unacceptable if the only changes suggested were the addition of Adcal-D₃ in all patients. The protocol set out what had been agreed by the parties. The complainant had not demonstrated on a balance of probabilities that either of these options were so.

The protocol required the GP to authorize the pharmacist to complete the practice computer repeat medication changes requested. The template letters stated 'Provided as a service to medicine by ProStrakan Ltd' at the end. The Panel considered it was not entirely clear from this wording what ProStrakan provided as a service to medicine.

The template letters included the instruction 'To be typed on Practice letterhead'. The Panel was concerned that the declaration of sponsorship, which appeared on the templates as a footer, below the item code number and the date of

preparation, would not be transcribed onto the final letter. There was no instruction as to the need to include this statement. In the Panel's view there was a strong possibility that letters had been sent without the declaration of sponsorship. However, in the absence of any evidence that this had happened, the Panel was obliged to rule no breach of the Code in this regard. Nonetheless, the Panel considered that the company had not maintained a high standard in this regard and a breach of the Code was ruled.

The Panel noted the documentation provided to the various parties was inconsistent in its description of the service at issue ie the material given to practices referred to a calcium and vitamin D supplementation clinical review whereas material for representatives and the pharmacist referred to a wider 'osteoporosis review'. The Panel further considered that the list of various supplements available (which appeared in the document given to practices) had not listed all in a fair-handed manner given that only the flavours of Adcal-D₃ had been listed; in the Panel's view whether there was a choice or not, it would be helpful, in terms of patient preference, for prescribers to know the flavours of the other calcium and vitamin D₃ supplements. Overall apart from a choice of formulation and strength there was also a choice of lemon, tutti-frutti, orange or peppermint flavours. The Panel thus considered that, with regard to the documents provided, high standards had not been maintained and a breach was ruled.

Notwithstanding its rulings above, the Panel was satisfied that the service would enhance patient care; it was not linked to the prescription of any specific medicine. The decision of what to prescribe lay with the patient's doctor. It was arguable whether the service was a therapy review as described in the supplementary information to the Code as its scope was very limited and the only assessment appeared to be whether or not certain patients were also prescribed calcium and vitamin D₃ supplements. However the Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breach of the Code was ruled.

An anonymous, non-contactable, general practitioner complained about an osteoporosis audit service offered by ProStrakan Group plc. ProStrakan marketed Adcal-D₃, a calcium and vitamin D₃ supplement.

COMPLAINT

The complainant explained that the audit service was offered as an Osteoporosis Project to enable better care of patients with osteoporosis. His practice had used a number of these types of services in the past and found them to be very useful. They had always focussed on patient care, whole disease areas and not on prioritising the

prescribing of one particular product. In this instance however he found himself in a very uncomfortable position with an expectation that he would prescribe only one product at the end – that which was promoted by ProStrakan.

The representative from ProStrakan first highlighted the service to him suggesting that it could benefit the practice, particularly with its large elderly population. It was also suggested that the process was approved by the local primary care trust (PCT) although the complainant was unable to verify this. The service was being delivered by an independent company which, it was claimed, would complete the service in the practice without any undue interference from ProStrakan. The complainant agreed to the service and signed the contract which stated that 'The service is not linked to the use of any particular product'. The protocol and guidelines referenced were nationally recognised criteria and all seemed very professional.

A pharmacist then completed a number of audits on the practice database to identify at-risk cohorts of patients. After this the complainant had a discussion with the pharmacist. Several points of this discussion were of concern and had prompted this complaint. After the conversation with the pharmacist the complainant was left with the following suggestions which made him feel uncomfortable:

- 1 Although the audits claimed to identify at-risk osteoporosis patients, they only looked to identify patients for Adcal-D₃. When the complainant asked if they could also consider bisphosphonates he was told that the company was not willing to fund an area where it did not have products. It was further suggested that the complainant could contact one of the providers of products in this area to request them to fund a review in this 'separate' area.
- 2 The pharmacist indicated that the expectation was that Adcal-D₃ would be prescribed in these patients and not any alternative product – as the review was being sponsored by ProStrakan.
- 3 The complainant was further told that the patient records had already been updated with the recommendations according to the protocol previously agreed with the ProStrakan representative. The complainant was told that he had to ensure that he signed to 'make it official'.
- 4 The complainant felt very uncomfortable but compelled to agree with the pharmacist as changes to patient records had already taken place – and actually the changes recommended did not compromise patient care.
- 5 The only changes to treatment that were suggested were the addition of Adcal-D₃ – in all patients.
- 6 When the complainant requested that the additional prescription medicine should be explained to patients personally by the pharmacist in either clinics or on the telephone, (as had happened in other audits that the practice conducted), he was told that there was not

enough funding for the service provider to spend the additional time and that the practice had to send out letters to patients and handle any reactive patient queries. The template letter provided did not refer to the service provider or to ProStrakan's support of the service.

This experience had severely dented the complainant's confidence in working with the pharmaceutical industry on these types of services, even with previously positive experiences – as such he felt compelled to complain. The explanation from ProStrakan regarding the service was clearly a very different brief to that given to the pharmacist who carried out the service. Having attended a recent introductory session to the Code he understood that companies were also responsible for the conduct of independent providers with whom they collaborated.

The complainant hoped that the Authority would be able to investigate and reassure health professionals working with pharmaceutical industry partners that services were based solely on improving patient care and not, as the complainant felt in this instance, to purely increase the prescription volume of a specific medicine.

When writing to ProStrakan, the Authority asked it to respond in relation to Clauses 2, 9.1, 9.10, 18.1 and 18.4 of the 2006 Code.

RESPONSE

ProStrakan was disappointed that the complainant had raised these issues anonymously as it would have valued the opportunity to conduct an in-depth investigation of such serious allegations. By choosing anonymity, in a case based entirely on hearsay, the complainant had prevented ProStrakan from refuting the claims made. Nevertheless, it had provided all the documentation that the Authority had requested and had endeavoured to highlight how these documents covered the issues raised. ProStrakan noted that the service provider had data on file that significantly supported ProStrakan's responses to these allegations. Due to the nature of this data (regarding the audit outcomes and prescribing habits of individual practices), ProStrakan did not have access to it. This data was referred to in the following text and could be provided direct to the Authority if required.

ProStrakan submitted that it had designed its therapy review service in collaboration with the service provider (which had significant expertise in such programmes). Pharmacists trained by the service provider carried out the audits in practices which had indicated their interest in the service. The practices were given results of the audit and were entirely at liberty to implement the recommendations or not. ProStrakan was not involved in the audit process, clinical review or implementation of prescribing or other changes.

ProStrakan noted that the complainant stated that it had been suggested that the process was approved by the local PCT although this had not been verified. ProStrakan was unable to comment on this due to the anonymity of the complainant.

- 1 Although the audits claimed to identify at-risk osteoporosis patients, they only looked to identify patients for Adcal-D₃. When the complainant asked if they could consider also bisphosphonates he was told that the company was not willing to fund an area where it did not have products. It was further suggested that the complainant should contact one of the providers of products in this area to request them to fund a review in this 'separate' area.

It was clear from the protocol that the audit identified a broad cohort of patients, in line with national guidance, and could provide a comprehensive list of patients who were at risk in a number of respects, beyond just identifying those who required supplementation. Section 2 of the protocol clearly allowed for consideration of additional therapy where required and appropriate, which could include bisphosphonates or other bone sparing therapies.

In the same section the practice could include any additional search criteria should it wish to specifically focus on, for example, bisphosphonate treatment.

The protocol did not suggest, let alone mandate, the use of a particular calcium and vitamin D supplement. Nine of the most commonly used supplements were listed, of which six were not ProStrakan's products.

ProStrakan believed that its protocol complied with Clause 18.4, in that the service would enhance patient care, and benefit the NHS. The protocol was based on current national guidance, and referred to the Scottish Intercollegiate Guidelines Network (SIGN) 71, which recommended a range of dosages of calcium and vitamin D, and not just that provided by Adcal-D₃. In this respect the protocol was relevant, current, robust, impartial and balanced, and therefore did not contravene Clause 2.

- 2 The pharmacist indicated that the expectation was that Adcal-D₃ would be prescribed in these patients and not any alternative product – as the review was being sponsored by ProStrakan.

The service was not linked to the use of any particular product, and in that regard ProStrakan noted the comprehensive list of product options in Section 2 of the protocol. The clinicians could make their own choice, or none at all. This last option was one which was exercised by 21% of practices reviewed within the last 6 months, according to the service provider.

In addition the protocol considered non-medicinal interventions, particularly where poor compliance

was encountered. Lifestyle advice and educational leaflets could be provided to these patients if requested by the authorising clinician. A copy of this leaflet was provided. If necessary, ProStrakan would be able to supply data on the quantities of patient education leaflets delivered to the service provider to support this intervention.

The protocol could provide a useful summary of the quality of prescribing for osteoporosis which could be used as an internal barometer of compliance with various national guidance or local guidelines.

Based on the protocol, and ProStrakan's brief to the service provider's pharmacists, and in the absence of specific detail permitting ProStrakan to investigate individual conduct, it strongly contested the likelihood of a pharmacist conducting him or herself in this manner, and further it claimed that its protocol and process complied with Clause 18.1, and that the protocol had not been offered as an inducement to prescribe Adcal-D₃.

- 3 The complainant was further told that the patient records had already been updated with the recommendations according to the protocol previously agreed with the ProStrakan representative. The complainant was told that he had to ensure that he signed to 'make it official'.

ProStrakan was unsure as to whether the complainant had alleged that its representative had colluded with the pharmacist to predetermine recommendations, or that the pharmacist had updated the patient records with the GP's choices before getting the GP's signature to authorise such changes.

ProStrakan's brief to its representatives clearly did not permit them to have more than a cursory interaction with the pharmacists, to facilitate an introduction to the practice. In the absence of specifics in this case, ProStrakan was unable to investigate or comment on this further.

The pharmacists, according to the protocol and brief, were unable to change patient medication unless authorised to do so (Section 5, part 1). Each individual patient required a review by the GP as detailed in Sections 4.3 and 4.4, following which, the GP might authorise various interventions including pharmacotherapeutic and/or other options. The pharmacist was unable to proceed without a signature to confirm that the GP had seen and reviewed the patient cohorts presented according to the agreed protocol.

The protocol and process did not permit the actions alluded to by the complainant, and ProStrakan believed it unlikely that a pharmacist would risk his or her professional standing in doing so. In the absence of specifics ProStrakan could not investigate the matter to this level of detail. ProStrakan therefore believed that Clauses 2 and 9.1 had not been breached.

- 4 The complainant felt very uncomfortable but was compelled to agree with the pharmacist as changes had already taken place – and actually the changes did not compromise patient care.

ProStrakan referred to its response at point 3 above.

- 5 The only changes to treatment that were suggested were the addition of Adcal-D₃ in all patients.

As mentioned in point 2 above, it was clear that the protocol and its various choices and options were discretionary, and entirely within the control of the clinician, and that they had to authorise any change or addition to medication, or provision of non-drug related information, for each patient. The GP and practice also retained the right to conduct these changes themselves, or not to participate in the process at all. Once again, the service provider had data that demonstrated the full variety of outcomes that occurred following use of the service.

- 6 When the complainant requested that the additional prescription medicine should be explained to patients personally by the pharmacist in either clinics or on the telephone (as had happened in other audits that the practice conducted), he was told that there was not enough funding for the service provider to spend the additional time and that the practice had to send out letters to the patients and handle any reactive patient enquiries. The template letter did not refer to the service provider or to ProStrakan's support of the service'.

Section 4.10 of the project protocol stated that any changes or additions to medication would be communicated to each patient along with further instructions if required, in accordance with the wishes of the individual practice. Although most practices requested patient communication by letter, others might request the sort of service requested by the complainant and these would be offered. In the absence of specific detail it was impossible to comment further.

Template letters were included in the documentation pack and clearly contained visible lettering in the footer that they and the service had been provided by ProStrakan, in compliance with Clause 18.4.

The service provider regularly inspected review services in progress to ensure compliance of its pharmacists with protocols, process, and conduct. In particular Code compliance and professional conduct with respect to the Medicines, Ethics and Practice Guide for Pharmacists (Royal Pharmaceutical Society of Great Britain) was inspected. ProStrakan believed that the employees conducted themselves in an appropriate and professional manner, and in the absence of specifics due to the complainant's anonymity, it was impossible for the service provider, to conduct an internal investigation around most of the

allegations made and therefore impossible for ProStrakan to respond to detail about the alleged conduct of individuals.

In conclusion, due to the complainant's anonymity, ProStrakan had been unable to investigate this matter as fully as it would have liked, or to respond to specific and extremely serious allegations which involved either one of its representatives or a pharmacist from the service provider. ProStrakan had provided documentation relating to the service, and an explanation of the processes and governance by the service provider to ensure compliance to the Code and the Medicines, Ethics and Practice Guide for Pharmacists. It was ProStrakan's view that it had not breached Clauses 2, 9.1, 9.10, 18.1 or 18.4.

FURTHER RESPONSE

In response to a request ProStrakan stated that it had not forwarded copies of the detail aid used in Adcal-D₃ sales visits. The detail aid contained no information regarding the therapy review service.

In relation to literature to be left with a customer, referred to in the sales force briefing document, ProStrakan stated that this was an oversight, as it had never had literature describing the service to be used as a leavepiece. This statement had been removed from the latest version of the document, which was currently in the approval process.

In relation to an enquiry as to why flavours of Adcal-D₃ were included in a table listing calcium and vitamin D₃ supplements, but not the flavours of the other supplements, ProStrakan stated that each Adcal-D₃ variant had this information as part of its registered name, held its own marketing authorization, and was prescribed as per the registered name of the formulation. ProStrakan had included a comprehensive list of available supplements and this included the variants of Adcal-D₃. It would not have been appropriate to simply refer to the Adcal-D₃ range as Adcal-D₃ due to there being different marketing authorizations. In addition, the other supplements on the market existed as single products, with one flavour. ProStrakan had listed these products by their registered names.

In relation to a request for a breakdown of the percentage of practices which following the service used Adcal-D₃ or ProStrakan product, other companies' calcium/vitamin D supplements or did not change patients' treatment, ProStrakan stated that as stated above, due to the nature of this data (regarding the audit outcomes and prescribing habits of practices), it did not have access to it.

ProStrakan had contractually agreed to pay the service provider a flat rate per day in implementation of the audit. ProStrakan did not pay, nor had it ever paid, bonuses of any description to that company or its employees

The choice of supplement was entirely at the discretion of the clinician and was made without input or direction from the therapy review team. Likewise, the clinician was free to choose any number of supplements to meet different patient needs, or to prescribe no therapy at all. The clinician was at liberty to change their decisions at any stage of the process without giving any reason or prior notification. The clinician was equally free to alter their choices at any time once the therapy review was complete.

ProStrakan was concerned that a complaint based entirely on hearsay from an anonymous GP regarding the alleged conduct of an unnamed pharmacist working on its behalf was becoming a general investigation of ProStrakan materials and working practices. Whilst ProStrakan had nothing to hide, it did not believe this would be appropriate or relevant to the complaint.

As an organisation, ProStrakan took issues of Code compliance extremely seriously. It was therefore frustrated that it was not able to fully examine and respond to this anonymous and unsubstantiated complaint.

In response to a further enquiry as to the percentage of practices which, following the service, used Adcal-D₃ or other ProStrakan product, other companies' calcium/vitamin D₃ supplements or did not change patients' treatment, the service provider replied on behalf of ProStrakan. It stated that of practices audited within the last six months, 79% initiated patients onto their preferred treatment. The other 21% chose to make changes to patients' treatment themselves or not to make any changes at all.

ProStrakan advised that it did not market any product other than Adcal-D₃ which was relevant to osteoporosis care or prevention.

PANEL RULING

The Panel noted that as the complainant was anonymous and non-contactable it was not possible for ProStrakan to respond in detail to the specific points raised about the audit.

The Panel considered that much would depend on the practice which had control of the process. The protocol required signatures before any audit could start. The practice could decide what action to take. It was vital that the pharmacists conducting the audit on behalf of ProStrakan followed the protocol as well as complying with their professional code. There was no evidence that they had not done so.

The Panel did not consider that the service was an osteoporosis audit service as mentioned by the complainant and as stated in some of the documentation from ProStrakan. The document describing the service to prescribers was entitled 'Calcium and Vitamin D Supplementation Clinical

Review Protocol'. The practice authorization form referred to a 'calcium and vitamin D₃ Deficiency Clinical Review'. It was confusing as the representatives' briefing note referred to an 'Osteoporosis Review' and a chart summarising the operation of the service was headed 'Osteoporosis Therapy Review Service'. The Pharmacist Briefing Document also referred to the service as an 'Osteoporosis Therapy Review Service'. The Panel was concerned that the documentation misnamed the service. It was likely that the representative had referred to an osteoporosis review service and this had contributed to the confusion.

The Panel noted that the protocol listed calcium and vitamin D₃ supplements in alphabetical order and gave details of their formulation and strength. Doctors were to indicate their preferred product and to decide whether an initial prescription should be raised and sent to patients. The first two products identified were Adcal-D₃ and Adcal-D₃ Dissolve respectively. The Panel noted that the formulation column listed 'Chewable Tab Lemon Tutti Frutti' for Adcal-D₃. The only details for all the other products, including Adcal-D₃ Dissolve, were 'Effervescent Tab', 'Chewable Tab' or 'Sachet' as appropriate. The Panel noted ProStrakan's submission that the two flavours of Adcal-D₃ chewable tablets had been listed because such information was part of the registered name. Conversely, all of the other products were only available in one flavour and so no flavour was stated for these. This however, was not clear to the reader. Further, the Panel considered that ProStrakan's submission about the flavours of Adcal-D₃ and the registered product names was misleading. From the summaries of product characteristics (SPCs) the tutti-frutti tablets were called 'Adcal-D₃ Chewable tablets' and the lemon flavoured tablets were called 'Adcal-D₃ Lemon Chewable tablets'.

The Panel noted that if there was evidence to show that the pharmacist had indicated that the expectation was that Adcal-D₃ would be prescribed then this would have been unacceptable. Similarly it would be unacceptable if the only changes suggested were the addition of Adcal-D₃ in all patients. The protocol set out what had been agreed by the parties. The complainant had not demonstrated on a balance of probabilities that either of these options were so.

The protocol required the GP to authorize the pharmacist to complete the practice computer repeat medication changes requested. The template letters stated 'Provided as a service to medicine by ProStrakan Ltd' at the end. The Panel considered it was not entirely clear from this wording what ProStrakan provided as a service to medicine.

The template letters included the instruction 'To be typed on Practice letterhead'. The Panel was concerned that the declaration of sponsorship, which appeared on the templates as a footer, below the item code number and the date of preparation, would not be transcribed onto the final letter. There

was no instruction as to the need to include this statement. In the Panel's view there was a strong possibility that letters had been sent without the declaration of sponsorship. However, in the absence of any evidence that this had happened, the Panel was obliged to rule no breach of Clause 9.10. Nonetheless, the Panel considered that the company had not maintained a high standard in this regard and a breach of Clause 9.1 was ruled. The Panel requested that ProStrakan be reminded that since 1 November 2008 the provisions of Clause 9.10, and its supplementary information, of the 2008 Code applied. This stated that the declaration of sponsorship must accurately reflect the nature of the company's involvement.

The Panel noted the documentation provided to the various parties was inconsistent in its description of the service at issue ie the material given to practices referred to a calcium and vitamin D supplementation clinical review whereas material for representatives and the pharmacist referred to a wider 'osteoporosis review'. The Panel further considered that the list of various supplements available (which appeared in the document given to practices) had not listed all in a fair-handed manner given that only the flavours of Adcal-D₃ had been listed; in the Panel's view whether there was a choice or not, it would be helpful, in terms of patient preference, for prescribers to know the

flavours of the other calcium and vitamin D₃ supplements. Overall apart from a choice of formulation and strength there was also a choice of lemon, tutti-frutti, orange or peppermint flavours. The Panel thus considered that, with regard to the documents provided, high standards had not been maintained and a breach of Clause 9.1 was ruled.

Notwithstanding its rulings above, the Panel was satisfied that the service would enhance patient care; it was not linked to the prescription of any specific medicine. The decision of what to prescribe lay with the patient's doctor. It was arguable whether the service was a therapy review as described in the supplementary information to Clause 18.4 as its scope was very limited and the only assessment appeared to be whether or not certain patients were also prescribed calcium and vitamin D₃ supplements. However the Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breach of Clauses 18.1 and 18.4 was ruled. The Panel also ruled no breach of Clause 2 which was reserved for use as a sign of particular censure.

Complaint received 16 October 2008

Case completed 23 December 2008

NURSE v SCHERING-PLOUGH

Alleged breach of confidentiality

A nurse complained about her suspension from a service provider in connection with an infusion service facilitation (ISF) nurse advisor programme carried out on behalf of Schering-Plough.

The complainant stated that she was suspended because she refused to give confidential information regarding her customers after the customers had signed confidential agreements. The complainant felt that her registration and code of conduct were being compromised and that this was against what the ABPI stood for. She had documentation and witness statements. This information was then going to be passed onto Schering-Plough.

The complainant explained that the programme was 'sold in' by the nurses who asked the consultant if they could review the unit and give feedback regarding staff and equipment etc used. This was for the unit to identify any issues and any changes needed to help increase efficacy for the patients and staff. This information was to be left on the unit and the only reports that went back to Schering-Plough were: number of units attended, number of introductory meetings, number of multi-disciplinary meetings completed and number of follow-up meetings.

At no time was any other information to be given to either the service provider or Schering-Plough (as per consent form).

Then the nurses were asked by their manager and the directors at the service provider to give all the information in the spreadsheets without the units' consent and a report would be given to Schering-Plough. (The complainant saw evidence of this report but did not have the documentation.) Six nurses resigned because their code of conduct was compromised and as the complainant spoke up for all of them and refused to give the information she was suspended but with backing from the Royal College of Nursing (RCN) she decided to resign rather than work for such an unethical company. The complainant submitted that she had never done anything like this before but felt so strongly for her customers and patients' confidentiality she felt she must make a stand.

The detailed response from Schering-Plough is given below.

The Panel noted that the intent of the programme was to benefit the NHS and maintain patient care by providing an assessment, service development and educational programme to support secondary care physicians with the care and management of patients receiving intravenous biologic therapies

within gastroenterology, rheumatology and dermatology. The unit agreement, which had to be signed by the ISF programme nurse advisor and the clinical director, or other authorised signatory, of the unit stated that '... the ISF Nurse will keep confidential all hospital and patient identifiable data to which he/she may have access during the provision of the ISF Programme'.

The Panel noted that the service provider had stated that, contrary to the complainant's submission, no other nurse advisor had resigned citing breaches of the Nursing and Midwifery Council (NMC) Code of Conduct as a reason. This company also submitted that the complainant was not suspended for refusing to supply confidential information in contravention of NMC Code or because she 'stood up' for colleagues in a similar position. The service provider further submitted that none of its nurse advisors had ever been required to disclose patient or unit identifiable data in contravention of any relevant codes or agreements with accepting NHS units. The Panel noted that there was a difference of opinion regarding the circumstances of the complainant's termination of employment.

The Panel noted that the agreement between Schering-Plough and the service provider was clear about the need to ensure that all confidential information was only disclosed to those who required the information for meeting the agreement and compliance with all applicable data privacy laws. The ISF Executive Summary made it clear that any associated data from the programme would only be reported to Schering-Plough in an aggregated, anonymised format with initial agreement from the participating unit. The service provider stated that it had, on occasion, received hospital identifiable data from nurse advisors but this was not required, requested or encouraged. There was no detail of any action taken by the service provider to remind nurses that the provision of such data was contrary to the unit agreement. The service provider stated that if it received hospital-identifiable data from the nurses then all reference to individual hospitals was removed before the data was stored. Hospital-identifiable or patient-identifiable data was never disclosed to Schering-Plough.

The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The Panel considered that the allegation was a serious one; however it did not consider that evidence had been provided to show that on the balance of probabilities Schering-Plough had required data that would identify either hospitals or patients to be supplied. Thus the Panel ruled no breach of the Code.

A nurse complained about her suspension from a service provider in connection with an infusion service facilitation nurse adviser programme carried out on behalf of Schering-Plough Ltd.

COMPLAINT

The complainant stated that she was suspended because she refused to give confidential information regarding her customers after the customers had signed confidential agreements.

As a nurse the complainant felt that her registration and code of conduct were being compromised and that this was against what the ABPI stood for. She had documentation and witness statements.

This information was then going to be passed onto Schering-Plough.

The complainant explained that the programme was 'sold in' by the nurses who asked the consultant if they could review the unit and give feedback to the unit regarding staff and equipment etc used. This was for the unit to identify any issues and any changes needed to help increase efficacy for the patients and staff. This information was to be left on the unit and the only reports that went back to Schering-Plough were: number of units attended, number of introductory meetings, number of multi-disciplinary meetings completed and number of follow-up meetings.

At no time was any other information to be given to either the service provider or Schering-Plough (as per consent form).

Then the nurses were asked by their manager and the directors at the service provider to give all the information in the spreadsheets without the units' consent and a report would be given to Schering-Plough. (The complainant saw evidence of this report but did not have the documentation.) Six nurses resigned because their code of conduct was compromised and as the complainant spoke up for all of them and refused to give the information she was suspended but with backing from the Royal College of Nursing (RCN) she decided to resign rather than work for such an unethical company. The complainant submitted that she had never done anything like this before but felt so strongly for her customers and patients' confidentiality she felt she must make a stand.

When writing to Schering-Plough, the Authority asked it to respond in relation to Clauses 2, 9.1 and 18.4 of the 2006 Code of Practice.

RESPONSE

Schering-Plough stated that it had reviewed the documentation provided in the matter and took the view that it disclosed no breach of Clauses 2, 9.1

and 18.4 for the reasons set out below.

Schering-Plough explained that it had engaged an independent third party to provide defined services. The programme referred to was the 'Infusion Service Facilitation (ISF) Programme'.

Under the programme, the service provider's nurse advisors collected information about 'patient journeys' ie the experience of patients receiving infusions of biological medicines. The results from each unit were then used to identify potential areas for reducing bottlenecks in the process, thus enhancing the efficiency of NHS infusion services, and to improve the patients' experience of infusions. The intention was to improve the care and management of patients in accordance with local or national guidelines.

The ISF Programme was carried out by the nurse advisors who collected and collated information from specific units, typically infusion centres in hospitals and acted as facilitator for multi-disciplinary teams from the units concerned in reviewing the results of the analysis.

The services under the ISF Programme were based on Improvement Leaders' Guides on service redesign issued by the NHS Institute for Innovation and Improvement. Copies of the guides were provided.

The scope of the services provided were set out in the contract dated 12 December 2007. A redacted copy of the contract was provided.

The contract was entered into following negotiations between the service provider and Schering-Plough. Before signature, the contracts and the underlying ISF Programme were reviewed by internal and external lawyers and certified through Schering-Plough's formal certification process. Schering-Plough understood that a similar approval process was followed by the service provider.

Confidentiality was specifically dealt with in the programme documentation as follows:

- Clause 5 of the contract required compliance by both parties with data privacy laws and regulations. It also specified that neither party was permitted to transfer or otherwise make known '*the names or other personal data provided to it by the other party*'.
- A standard operating procedure (SOP) was included as an appendix to the contract, which regulated the manner in which the services were to be provided. In particular, the SOP specified at clause 7.2, that, '*[no] patient identifiable data will be collected...*'.
- One of the template agreements relating to the SOP was the Unit Agreement. It was the only reference to hospital identifiable data in the programme. A copy of the unit agreement template was supplied by the complainant to the

Authority. This was an agreement entered into between the service provider and the unit before any services were provided under the programme. It specified that the nurse advisor would not have access to patient notes. It also specified that '*in accordance with the Data Protection Act 1998...*' the nurse advisor will '*keep confidential all hospital and patient identifiable data*'. Schering-Plough noted that the Data Protection Act 1998 only applied to personal data and did not extend to organisations. Despite that, it was clear that the parties intended that the names of the units involved in the programme would not be made public. Indeed, at no point were any details identifiable to any unit passed to Schering-Plough.

As the allegations related to activities undertaken on Schering-Plough's behalf by the service provider, Schering-Plough believed that its direct evidence in this matter was likely to be helpful. A summary of its key points in response to the complaint was provided. Schering-Plough believed that the summary clearly set out the position of Schering-Plough and the service provider on this matter. Schering-Plough also had the following comments:

- Schering-Plough was aware of the need to retain the anonymity of the units. Many units valued the assistance received under the programme and the opportunity to discuss the results with a view to identifying bottlenecks and potential improvements. However, it was felt that units would be less willing to take part in such a programme if poorly performing units were to be publicly named or if the results were to be presented in a competitive ranking. Likewise, if the programme were to be regarded by the units as a quasi-audit, they might inappropriately seek to 'improve' their outcomes, which could undermine the whole purpose of the programme. In view of that, it would not be in the interests of Schering-Plough or the service provider to record or disclose such details.
- The nurse advisors were trained on the ISF programme before its commencement. Part of that training related to the need for the nurse advisors to ensure that the unit agreements were signed before they carried out any services at the unit. As such, it would be the nurse advisor's obligation to anonymise the patient identifiable data and hospital identifiable data. Schering-Plough had never requested, seen or had access to any hospital identifiable data.
- Schering-Plough noted that the complaint related specifically to the alleged disclosure of the identity of the units concerned to the service provider and not patient identifiable data. Even if that allegation was true, which Schering-Plough denied, such information would not amount to 'personal data' under the Data Protection Act 1998. The Act defined 'personal data' as 'data which related to a *living individual* who could be identified – (a) from those data, or (b) from those

data and other information which was in the possession of, or was likely to come into the possession of, the data controller' (emphasis added). There was no breach of the provisions of the Act or of patient confidentiality and thus no breach of Clause 18.4.

Schering-Plough submitted that with reference to Clause 9.1, high standards had been maintained. The nurse advisors were trained on all aspects of the ISF programme, including obligations relating to confidentiality. The nurse advisors were aware of the need to anonymise data. If they failed to do so, the service provider would anonymise the data in any event, so no hospital identifiable data were recorded.

Under Clause 18.4, this was a programme which enhanced patient care or benefited the NHS and maintained patient care. It had been provided with due regard to Clause 18.1 and did not constitute an inducement to prescribe. The programme was not product related and sought to enhance patient care in a manner completely aligned with the NHS agenda.

With regard to Clause 2, programmes such as this were pivotal to enhancing the reputation of the industry with the NHS. No hospital identifiable data were disclosed to Schering-Plough. On that basis, there had been no breach of this clause.

Schering-Plough denied that there had been any breach of the Code or any data protection or privacy law. All the relevant provisions of the internal SOP had been followed by the service provider.

Schering-Plough noted that any grievance raised by the complainant and any disciplinary proceedings appeared to be purely an employment matter between the complainant and the service provider and were not ones which related to the Code, the law or Schering-Plough.

PANEL RULING

The Panel considered that as the service was provided as a medical or educational good or service the matter was subject to the Code. The intent of the programme was to benefit the NHS and maintain patient care by providing an assessment, service development and educational programme to support secondary care physicians with the care and management of patients receiving intravenous biologic therapies within gastroenterology, rheumatology and dermatology. The unit agreement, which had to be signed by the ISF programme nurse advisor and the clinical director, or other authorised signatory, of the unit stated that '... the ISF Nurse will keep confidential all hospital and patient identifiable data to which he/she may have access during the provision of the ISF Programme'.

The Panel noted that the service provider had stated

that, contrary to the complainant's submission, no other nurse advisor had resigned citing breaches of the Nursing and Midwifery Council (NMC) Code of Conduct as a reason. This company also submitted that the complainant was not suspended for refusing to supply confidential information in contravention of NMC Code or because she 'stood up' for colleagues in a similar position. The service provider further submitted that none of its nurse advisors had ever been required to disclose patient or unit identifiable data in contravention of any relevant codes or agreements with accepting NHS units. The Panel noted that there was a difference of opinion regarding the circumstances of the complainant's termination of employment.

The Panel noted that the agreement between Schering-Plough and the service provider supporting the ISF programme was clear about the need to ensure that all confidential information was only disclosed to those who required the information for meeting the agreement and compliance with all applicable data privacy laws. The ISF Executive Summary made it clear that any associated data from the programme would only be reported to Schering-Plough in an aggregated, anonymised format with initial agreement from the

participating unit. The service provider stated that it had, on occasion, received hospital identifiable data from nurse advisors but this was not required, requested or encouraged. There was no detail of any action taken by the service provider to remind nurses that the provision of such data was contrary to the unit agreement. The service provider stated that if it received hospital-identifiable data from the nurses then all reference to individual hospitals was removed before the data was stored. Hospital-identifiable or patient-identifiable data was never disclosed to Schering-Plough.

The Panel noted that the complainant had the burden of proving their complaint on the balance of probabilities. The Panel considered that the allegation was a serious one; however it did not consider that evidence had been provided to show that on the balance of probabilities Schering-Plough had required data that would identify either hospitals or patients to be supplied. Thus the Panel ruled no breach of Clauses 2, 9.1 and 18.4.

Complaint received **20 October 2008**

Case completed **23 December 2008**

ANONYMOUS v GLAXOSMITHKLINE

Patient outcomes and information service

An anonymous and non-contactable complainant enquired whether the patient outcomes and information service (POINTS) offered by GlaxoSmithKline was within the Code. There was a complex authorization form. Did people really know what they were signing? The complainant thought that it had to be signed for each report. Why had some PCTs banned it? Was GlaxoSmithKline being honest with its staff and customers? It looked like a monitoring tool for the representative. How could users be sure that the data were not seen by their local Seretide representatives? The person offering the service was the Seretide representative last year. They had had a nurse in previous years. Where had she gone? The complainant refused the service and other support had disappeared (spirometry training and staff training to run reports).

The detailed response from GlaxoSmithKline is given below.

The Panel noted that explanatory notes which accompanied the POINTS authorization form stated that the service would be provided on the understanding that the participating doctor agreed that it was in the best medical interests of patients and that the doctor would retain complete control of the service at all times. It was further stated that the provision of POINTS was separate from the prescription, supply, administration, recommendation or promotion of specific medicines and all written material provided in association with the service would be non-promotional. The explanatory notes also stated no individual would be identifiable from the data sent from the practice. There was no evidence that POINTS was a monitoring tool for Seretide representatives or that data was seen by Seretide representatives as alleged.

The Panel considered that the roles of the GlaxoSmithKline promotional staff and non-promotional Respiratory Care Associates (RCAs) appeared to be clearly separated. When the representatives promoted medicines they did not discuss individual services although they might introduce the local RCA to the practice. None of the RCA activities nor other GlaxoSmithKline activities were contingent upon the uptake of POINTS.

The Panel considered that much would depend on the practice which had control of the process. It did not appear to the Panel that the arrangements were in general unacceptable.

The Panel noted that some PCTs had refused the POINTS service, not because of the service *per se*,

but due either to incompatibility of software or to local IT policies.

The complainant had provided no evidence to show that a refusal to accept the POINTS service had led to other GlaxoSmithKline-sponsored support being withdrawn. The Panel noted that the complainant's anonymity would not have allowed GlaxoSmithKline to investigate this allegation further. The Panel noted GlaxoSmithKline's submission that practices which declined to participate in POINTS continued to be eligible for all other services from GlaxoSmithKline.

Overall the Panel considered that the service offered was not unacceptable; it would enhance patient care. The provision of the service was not linked to the prescription of any specific medicine. The decision of what to prescribe lay with the patient's doctor. The Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breach of the Code was ruled.

An anonymous and non-contactable complainant complained about the patient outcomes and information service (POINTS) offered by GlaxoSmithKline UK Ltd.

COMPLAINT

The complainant enquired whether POINTS was within the Code.

There was a complex authorization form. Did people really know what they were signing? The complainant thought that it had to be signed for each report.

A primary care trust (PCT) in the South East and other PCTs around the county had banned it. Why? The representative looked most uncomfortable when asked. Was GlaxoSmithKline being honest with its staff and customers?

It looked like a monitoring tool for the representative. How could users be sure that the data were not seen by their local Seretide representatives? Indeed the person offering the service was the Seretide representative last year. They had had a nurse in previous years. Where had she gone?

The complainant refused the service and other support had disappeared (spirometry training and staff training to run reports).

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 2, 9.1, 18.1 and 18.4 of the 2006 Code.

RESPONSE

GlaxoSmithKline regretted that a health professional was concerned about POINTS and felt confused or uncomfortable about it. GlaxoSmithKline believed POINTS was a valuable service to patients and the NHS and that it was in keeping with both the letter and the spirit of the Code; specifically the company denied a breach of Clauses 2, 9.1, 18.1 or 18.4.

Overview

POINTS was a software based audit tool provided in the interests of patients and the NHS. It aimed to improve the standards of care for COPD patients in areas with a higher than average disease burden and it was consistent with national guideline recommendations. POINTS was sponsored by GlaxoSmithKline and provided as a service to medicine by its Respiratory Care Associates (RCAs), an entirely non-promotional team. A third party was involved in the set-up and running of the service.

Rationale for POINTS

Patients with complex long-term progressive conditions, such as COPD, benefited from regular structured review as part of their long-term management.

Audit was a well established and encouraged method of assessing practice performance in relation to local or national guidance, and allowed practices to identify areas where there was scope for improvement on the existing standard of care. POINTS was an audit tool which allowed practices to do this and could be tailored to meet practice needs; furthermore it allowed 're-audit' so that the impact of interventions made within the practice could be evaluated.

The National Institute for Health and Clinical Excellence (NICE) guidelines for the management of COPD (2004), recommended that 'health care commissioning organisations consider using patient-centred audit intermittently, to investigate the totality of services and identify particular areas that needed further development'.

POINTS

POINTS was a software package which provided an automated audit and analysis of practice records. The software had been developed by an independent computer software company. A third party installed the POINTS software and analysed

the data to produce practice specific reports.

POINTS contract

- The contract for the service was held between the practice, a third party and GlaxoSmithKline and clearly outlined the responsibilities of all parties involved and covered important information including data protection; as a result it was a detailed and complex legal document. The most important function of the contract was to ensure that patients' interests were protected.

POINTS software

- If a practice chose to use POINTS, the software was installed, usually remotely onto the practice computer system. If the practice computer did not allow remote installation, then a technician would visit the practice and upload the software manually.

POINTS reports

- A baseline report was generated when the POINTS software was installed. This enabled the practice to assess the demographics and management of its COPD population, and to identify areas where there was inadequate data collection. The data included in the report were consistent with the NICE COPD guidelines.
- The baseline report was prepared by the third party and sent to the RCA. The RCA delivered the report to the practice and provided support in interpreting the report and the significance of any findings. Data which could identify individual patients were not included in the report.
- Further reports were generated in a similar fashion. Practices could decide the interval between reports and the period over which the audit tool was available. These reports were compared to the baseline report enabling the practice to assess the impact of measures which it had created and chosen to implement. Interpretation of reports could be complex; the RCA remained available to support the practices at this stage. As of 1 September 2008 a new contract (authorization form) was produced for each report generated.

Patient confidentiality

- The data sent to GlaxoSmithKline and the third party did not contain named patient or patient identifiable information. Identifiable patient information was held only on the practice computer systems. It was made clear to practices and to RCAs that patient identifiable information was not to be seen by GlaxoSmithKline staff at any time.

Respiratory Care Associates (RCAs)

POINTS was only offered by RCAs.

- RCAs were non-promotional representatives who delivered education and services to improve the care of COPD patients. They did not undertake any promotional activities. They were provided with separate materials, training, and objectives to the promotional representatives. RCAs had specific managers who did not manage the promotional representatives. RCAs were not remunerated on and did not participate in a bonus scheme which was based upon the sales of a single medicine, brand or therapy area. The service was separate from the prescription, supply, administration, recommendation or promotion of specific medicines and RCA materials did not bear the name of any medicine.
- Support which the RCA could offer to a practice included:
 - Hospital episode statistics reports
 - Educational input (workshops and support for diploma qualifications)
 - Protocol development (including anonymised patient notes review)
 - Patient review (including clinic support and screening services)
 - Audit (POINTS)

The RCA team focussed on areas where maximum patient and practice benefit would be achieved. Therefore practices with higher than average COPD prevalence or list sizes were targeted. A briefing document, sent to all RCA managers on 12 August 2008, which explained how to use the current 'Targeting and Segmentation' spreadsheet was provided. GlaxoSmithKline also offered to provide the spreadsheet database of practices should the Authority wish to review it.

- Practices were not targeted on market share or prescribing of GlaxoSmithKline medicines or indeed any other medicines. Activities that RCAs undertook were educational and services to medicine, as such other practices were entitled to request RCA services if they considered that they would improve the existing level of care at their practice.
- The local RCA might be introduced to a practice by the promotional representative, however the promotional representative did not discuss individual services that the RCA could provide. The promotional representative was not present whilst these services were discussed or delivered.
- RCAs underwent comprehensive training on appropriate communication between promotional and non-promotional representatives. This policy applied to all working relationships including, but not limited to, POINTS. Specifically, RCAs were briefed that they

'must not share information about individual customers' prescribing habits or beliefs'.

- The RCA support to the practice was intended to help improve patient care. The RCA would also upskill the practice through education and tools such as POINTS, to help ensure that these benefits could be maintained. RCA services were provided for a period of time appropriate for the needs of the practice.

Training of RCAs relevant to POINTS

All RCAs received annual accredited therapy area training from independent educational bodies (Educational for Health and Respiratory Education UK) and had, or were working towards, diploma modules in COPD. All RCAs were trained on the provision of education, goods and services by the pharmaceutical industry.

Copies of the RCA training materials, briefing materials and materials to be used with practices were provided.

Provision of POINTS to a practice

Promotional teams were not provided with training or materials regarding POINTS. Promotional representatives did not offer POINTS. As a result, if a customer asked a promotional representative about POINTS the local RCA would answer the enquiry.

The RCAs had a number of services and educational materials which they could offer to enhance the management of COPD. The support they offered was tailored to the needs of the individual practice. POINTS might not be appropriate in a practice whose development needs were primarily educational.

None of the RCA activities were contingent upon the uptake of another service unless they were directly linked (for example training on POINTS reports would be inappropriate in a practice that was not using POINTS). Similarly, other GlaxoSmithKline activities were not contingent upon the uptake of POINTS.

POINTS was provided on the understanding that the practice considered that it was in the best medical interest of the patients; the practice retained full control of the service at all times.

POINTS might not be accepted by a practice or a PCT for a number of reasons such as a lack of computer facilities at the practice, POINTS software being incompatible with existing software or inadequate staffing resource. Similarly a practice which already had audit facilities was unlikely to benefit from POINTS.

Some PCTs had a policy that prohibited individual practices downloading 'non-PCT-approved'

software, or in some cases, working with the pharmaceutical industry on such activities. In these instances GlaxoSmithKline did not provide POINTS.

Summary

POINTS was an audit tool provided in the interests of patients and the NHS. It aimed to improve the standards of care for COPD patients in areas with a higher than average disease burden and it was consistent with national guidelines.

As evidenced by the supporting documentation, the service was not an inducement to prescribe, supply, administer or recommend any medicine. It did not bear the name of any medicine. The RCAs were comprehensively trained in COPD, POINTS and the appropriate provision of non-promotional services.

GlaxoSmithKline believed that the service complied with both the letter and the spirit of the Code; specifically it did not consider that it was in breach of Clauses 2, 9.1, 18.1 or 18.4.

In response to a request for further information, GlaxoSmithKline noted that it had been asked to respond specifically to the complainant's comments "... that a PCT in the South East and other PCT's around the country had banned POINTS'. GlaxoSmithKline stated that it was unclear what 'banned' referred to in this context as, to its knowledge, no PCT had banned POINTS due to a perceived problem with the service. GlaxoSmithKline did not record why any individual practices declined POINTS and would not expect RCAs to probe around the reasons behind such a decision.

POINTS software was compatible with the majority of practice systems but not all. If the software in a region was not compatible then the PCT might advise its practices not to install third party software and this was what had happened in the PCT named by the complainant. GlaxoSmithKline submitted that this did not represent a 'ban' of POINTS, but reflected the fact that software systems were simply not compatible. Similarly other areas had specific IT policies to restrict the type of software installed on a practice computer or the method of installation. It was not always possible to provide POINTS in a way which would meet local policies but, as above, GlaxoSmithKline did not consider that this represented a ban on POINTS.

The POINTS audit tool had been successfully used in over 1,350 practices. Whilst there had been occasional technical challenges setting up the software in an individual practice, GlaxoSmithKline had never had a complaint about the quality or the running of the service. No practice or PCT had stopped using POINTS as a result of being dissatisfied.

In relation to the availability of GlaxoSmithKline services to practices that declined participation in POINTS, GlaxoSmithKline stated that practices which declined to participate in POINTS continued to be eligible for all other services from GlaxoSmithKline.

PANEL RULING

The Panel noted that the complainant appeared generally unhappy about the arrangements for the POINTS service. The complainant was critical of the complexity of the authorization form and suggested that POINTS was a monitoring tool for representatives. The fact that some PCTs had 'banned' POINTS was noted and it was implied that a refusal to accept the POINTS service would lead to other GlaxoSmithKline-sponsored support being withdrawn.

The Panel noted that explanatory notes which accompanied the POINTS authorization form stated that the service would be provided on the understanding that the participating doctor agreed that it was in the best medical interests of patients and that the doctor would retain complete control of the service at all times. It was further stated that the provision of POINTS was separate from the prescription, supply, administration, recommendation or promotion of specific medicines and all written material provided in association with the service would be non-promotional. The explanatory notes also stated that neither GlaxoSmithKline nor the third party would be able to identify any individual from the data sent from the practice. There was no evidence that POINTS was a monitoring tool for Seretide representatives nor that data was seen by Seretide representatives as alleged.

The Panel considered that the roles of the GlaxoSmithKline promotional staff and non-promotional staff (RCAs) appeared to be clearly separated. When the representatives promoted medicines they did not discuss individual services although they might introduce the local RCA to the practice. None of the RCA activities nor other GlaxoSmithKline activities were contingent upon the uptake of POINTS.

The Panel considered that much would depend on the practice which had control of the process. It did not appear to the Panel that the arrangements were in general unacceptable.

The Panel noted GlaxoSmithKline's explanation as to why some PCTs had refused the POINTS service ie it was not because of the service *per se* but due either to incompatibility of software or to local IT policies which did not allow the installation of third party software.

The complainant had provided no evidence to show that a refusal to accept the POINTS service had led to other GlaxoSmithKline-sponsored

support being withdrawn. The Panel noted that the complainant's anonymity would not have allowed GlaxoSmithKline to investigate this allegation further. The Panel noted GlaxoSmithKline's submission that practices which declined to participate in POINTS continued to be eligible for all other services from GlaxoSmithKline.

Overall the Panel considered that the service offered was not unacceptable; it would enhance patient care. The provision of the service was not linked to the prescription of any specific medicine.

The decision of what to prescribe lay with the patient's doctor. The Panel did not consider that the service was an inducement to prescribe, supply, administer, recommend or buy any medicine. No breach of Clauses 18.1 and 18.4 was ruled. The Panel also ruled no breach of Clauses 9.1 and 2.

Complaint received **21 October 2008**

Case completed **9 December 2008**

PHARMACIST HEAD OF PRESCRIBING TEAM v PFIZER

Lipitor mailing

A pharmacist head of prescribing team complained about a Lipitor (atorvastatin) mailing issued by Pfizer. The single A4 sheet was headed on both sides with 'Lipitor: an evidence-based choice for lowering cholesterol to improve cardiovascular outcomes'. The front page featured a bar chart showing the decrease in LDL-C from baseline with various doses of pravastatin, simvastatin, rosuvastatin and atorvastatin followed by 'Do you prescribe a treatment which has evidence of improved cardiovascular outcomes through cholesterol lowering?'. The results from various Lipitor trials in patients with moderate to high risk and high to higher risk were then stated. Overleaf it was stated that Lipitor had a wealth of published cardiovascular outcomes trials with 12 such trials for Lipitor, 2 for rosuvastatin, 1 for ezetimibe/simvastatin and none for ezetimibe.

The complainant's main concern was that the table of data stating the number of cardiovascular outcomes trials for Lipitor, rosuvastatin, ezetimibe/simvastatin and ezetimibe should also have listed simvastatin and pravastatin as there was a wealth of published data for these two medicines. The complainant alleged that the table gave a false impression of the current state of evidence relating to statins.

The detailed response from Pfizer is given below.

The Panel noted that the bar chart compared the efficacy of Lipitor with that of pravastatin, simvastatin and rosuvastatin. The Panel noted Pfizer's submission that generic statins, simvastatin, and some pravastatin, were used first line in over 90% of patients. The question below the bar chart 'Do you prescribe a treatment which has evidence of improved cardiovascular outcomes through cholesterol lowering?' implied that some treatments might not have evidence of improved cardiovascular outcomes. On turning the page readers were presented with a table which appeared to show that only Lipitor, rosuvastatin and ezetimibe/simvastatin had published cardiovascular outcomes data which was not so. The Panel noted Pfizer's submission that the purpose of the table was to demonstrate the number of published cardiovascular outcomes trials for therapies most likely to be considered alongside Lipitor as second line. This was not clear, particularly given that the bar chart on the front page compared Lipitor with, *inter alia*, the two first line statins. The Panel considered that the mailing was misleading as alleged. A breach of the Code was ruled.

A pharmacist head of prescribing team complained

about a Lipitor (atorvastatin) mailing (ref LIP3086) issued by Pfizer Limited. The single A4 sheet was headed on both sides with 'Lipitor: an evidence-based choice for lowering cholesterol to improve cardiovascular outcomes'. The front page featured a bar chart showing the decrease in LDL-C from baseline with various doses of pravastatin, simvastatin, rosuvastatin and atorvastatin. Below the chart readers were asked the question 'Do you prescribe a treatment which has evidence of improved cardiovascular outcomes through cholesterol lowering?'. The results from various Lipitor trials in patients with moderate to high risk and high to higher risk were then stated. Overleaf it was stated that Lipitor had a wealth of published cardiovascular outcomes trials. It was stated that there were 12 such trials for Lipitor, 2 for rosuvastatin, 1 for ezetimibe/simvastatin and none for ezetimibe.

COMPLAINT

The complainant's main concern was that the table of data stating the number of cardiovascular outcomes trials for Lipitor, rosuvastatin, ezetimibe/simvastatin and ezetimibe should also have listed simvastatin and pravastatin as there was a wealth of published data for these two medicines. The complainant alleged that the table gave a false impression of the current state of evidence relating to statins.

When writing to Pfizer, the Authority asked it to respond in relation to Clause 7.2 which was the same in the 2006 and 2008 Codes.

RESPONSE

Pfizer stated that the objective of the mailer was to promote the wealth of published cardiovascular outcomes evidence supporting Lipitor through effective cholesterol lowering.

In the UK generic statins (mainly simvastatin, occasionally pravastatin) were generally used first line over 90% of the time, in patients who required lipid lowering therapy. Pfizer agreed that generic statins had a large body of cardiovascular outcomes data. Branded statins such as Lipitor or Crestor (rosuvastatin), the addition of Ezetrol (ezetimibe) to a statin, or the simvastatin/ezetimibe combination therapy (Inegy) were generally used second line when greater lipid lowering efficacy was required than achieved with generic statins or when generic statins were poorly tolerated. The purpose of the table was to demonstrate the number of cardiovascular outcomes trials currently published

for these alternative lipid lowering strategies.

The table was not an exhaustive list of all lipid lowering therapies available, as it did not include generic statins, fibrates, nicotinic acid or bile acid sequestrants. It was intended to provide details of the current cardiovascular trial evidence for the therapies which were most likely to be considered alongside Lipitor.

For these reasons Pfizer did not believe it was in breach of Clause 7.2.

In response to a request for further information, Pfizer submitted that the mailing had been widely distributed in primary and secondary care including pharmacists, nurses, and doctors.

PANEL RULING

The Panel noted that on the front page of the mailing a bar chart compared the efficacy of Lipitor with that of pravastatin, simvastatin and rosuvastatin. The Panel noted Pfizer's submission that generic statins, simvastatin, with some

pravastatin, were used first line in over 90% of patients. The question below the bar chart 'Do you prescribe a treatment which has evidence of improved cardiovascular outcomes through cholesterol lowering?' implied that some treatments might not have evidence of improved cardiovascular outcomes. On turning the page readers were presented with a table which appeared to show that only Lipitor, rosuvastatin and ezetimibe/simvastatin had published cardiovascular outcomes data which was not so. The Panel noted Pfizer's submission that the purpose of the table was to demonstrate the number of published cardiovascular outcomes trials for therapies most likely to be considered alongside Lipitor as second line. This was not clear, particularly given that the bar chart on the front page compared Lipitor with, *inter alia*, the two first line statins. The Panel considered that the mailing was misleading as alleged. A breach of Clause 7.2 was ruled.

Complaint received 23 October 2008

Case completed 10 December 2008

ASSOCIATE DIRECTOR PHARMACY POLICY & PRESCRIBING v MERCK SHARP & DOHME AND SCHERING-PLOUGH

Ezetrol journal advertisement

The Associate Director Pharmacy Policy & Prescribing at a teaching primary care trust complained about an advertisement for Ezetrol (ezetimibe) in Pulse in September issued by Merck Sharp & Dohme and Schering-Plough.

The complainant noted the headline claim 'New NICE [National Institute for Health and Clinical Excellence] technology appraisal recommends ezetimibe alone or in combination with initial statin therapy'. The NICE technology appraisal cited in support of the claim, and stated in very small font size in a footnote to the prescribing information, was the NICE technical appraisal 132, November 2007 – Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. Those reading the advertisement, however might reasonably assume that the 'New' NICE guidance referred to was the Clinical Guideline 67 – Lipid Modification. This guideline clearly gave a very different (and much less significant) place in treatment for ezetimibe for lipid modification in primary and secondary prevention of cardiovascular disease than did technology appraisal 132. The advertisement did not refer to familial hypercholesterolaemia. The complainant alleged that the advertisement was misleading.

The detailed response from Merck Sharp & Dohme and Schering-Plough is given below.

The Panel noted that the headline to the advertisement stated 'New NICE technology appraisal recommends ezetimibe alone or in combination with initial statin therapy'. The cited reference was the NICE technology appraisal guidance 132 published in November 2007. The advertisement was published in September 2008. In May 2008 NICE had issued Clinical Guideline 67 on Lipid Modification. The advertisement was clearly about lipid control and the Panel considered that a reference to something 'new' from NICE might be assumed by some readers to be the document issued four months earlier (the clinical guideline) and not the document issued ten months previously (the technology appraisal). Nonetheless the heading clearly referred to the technology appraisal and so in that regard the Panel considered that the advertisement was not misleading and no breach was ruled.

The Panel noted that the technology appraisal guidance 132 (Ezetimibe for the treatment of

primary (heterozygous – familial and non-familial) hypercholesterolaemia) was solely about ezetimibe and its place in therapy. The medicine was recommended for use either alone or in combination with initial statin therapy. It was noted, however, that, *inter alia*, a clinical guideline on lipid modification was under development and that the technology appraisal guidance should be read in the context of the relevant clinical guideline when available. The lipid modification clinical guideline was published in May 2008.

The clinical guidance examined the whole therapy area and the use of lipid modification therapy, not just the use of ezetimibe. The clinical guideline was concerned with 'Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease'. In a section looking at treatment pathways for primary and secondary prevention it was stated that one of the treatment choices for patients who could not tolerate statins for primary prevention was ezetimibe. Readers were referred to the NICE technology appraisal guidance 132 for the treatment of primary (heterozygous-familial and non familial) hypercholesterolaemia. The clinical guideline was silent upon the use of combination therapy of any kind.

The Panel noted the complainant's comments that the clinical guideline gave a less significant place in treatment for ezetimibe in primary and secondary prevention than the technology appraisal. The two documents had to be considered together. The clinical guideline had not rendered the ezetimibe technology appraisal irrelevant. The advertisement at issue was about the use of Ezetrol not about the broad therapy area of lipid lowering. The Panel considered that it was true to state that, if and when ezetimibe was to be prescribed, NICE had recommended its use either alone or in combination with initial statin therapy. In that regard the Panel considered that the headline claim was not misleading as alleged and that it could be substantiated. No breach of the Code was ruled.

The Panel noted that the main part of the advertisement did not refer to familial hypercholesterolaemia; the indications for ezetimibe were stated in the prescribing information ie primary (heterozygous familial and non-familial) hypercholesterolaemia, homozygous familial hypercholesterolaemia and homozygous sitosterolaemia. The NICE technology appraisal

guidance referred to in the headline was about the use of ezetimibe for the treatment of primary-(heterozygous familial and non-familial) hypercholesterolaemia. The Panel considered that the prescribing information was adequate with regard to the stated use of ezetimibe and that the advertisement was not misleading in that regard. No breach was ruled.

The Associate Director Pharmacy Policy & Prescribing at a teaching primary care trust complained about an advertisement (ref 08-09 EZT.08.GB.751108.J) for Ezetrol (ezetimibe) in Pulse, 22 September, issued by Merck Sharp & Dohme Limited and Schering-Plough Limited.

COMPLAINT

The complainant noted the headline claim 'New NICE [National Institute for Health and Clinical Excellence] technology appraisal recommends ezetimibe alone or in combination with initial statin therapy'.

The NICE technology appraisal cited in support of the claim, and stated in very small font size in a footnote to the prescribing information, was the NICE technical appraisal 132, November 2007 – Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. Those reading the advertisement, however might reasonably assume that the 'New' NICE guidance referred to was the Clinical Guideline 67 – Lipid Modification. This guideline clearly gave a very different (and much less significant) place in treatment for ezetimibe for lipid modification in primary and secondary prevention of cardiovascular disease than did technology appraisal 132. The advertisement did not refer to familial hypercholesterolaemia.

The complainant alleged that the advertisement was misleading.

When writing to the companies, the Authority asked them to respond in relation to Clauses 7.2 and 7.4 of the Code which were the same in the 2006 and 2008 Codes.

RESPONSE

Merck Sharp & Dohme and Schering-Plough submitted a joint response.

The companies were surprised that the complainant found the advertisement to be misleading and that those reading the advertisement might reasonably assume that the 'New' NICE guidance referred to was the Clinical Guideline 67 - Lipid Modification, as the title '**NEW NICE TECHNOLOGY APPRAISAL**' [emphasis added] was very prominent; it was written in capital letters, bold type and font size and the statements and claims immediately below it were all taken from this official document.

Immediately after 'appraisal' a subscript '1' referred the reader to reference number 1, located at the end of the prescribing information. This reference clearly stated that the information related to NICE single technology appraisal of ezetimibe (November 2007). The reference was of the same font size as the prescribing information, namely a lower case 'x' was no less than 1mm in height. This was in accordance with the supplementary information to Clause 4.1, which stated that the prescribing information must be given in a clear and legible manner which assisted readability. By default, the same should hold true for the legibility of references. The Code, in any case, allowed for statements and claims to be made without the need for references - the only exception being where references were made to published studies (Clause 7.6).

In using the word 'New' the companies had taken into account Clause 7.11 which allowed the word 'New' to be used for any 'product, presentation or therapeutic indication' for a period of no longer than 12 months. As the complainant acknowledged, the technology appraisal was issued in November 2007, and the advertisement appeared in the 22 September 2008 edition of Pulse, so 'New' was used well within the 1 year timeframe allowed by the Code.

NICE classified its guidance according to type, which was given on its website as follows:

'Technology appraisals'

Technology appraisals are recommendations on the use of new and existing medicines and treatments within the NHS in England and Wales, such as:

- medicines
- medical devices (for example, hearing aids or inhalers)
- diagnostic techniques (tests used to identify diseases)
- surgical procedures (for example, repairing hernias)
- health promotion activities (for example, ways of helping people with diabetes manage their condition).

Clinical guidelines

Clinical guidelines are recommendations on the appropriate treatment and care of people with specific diseases and conditions within the NHS in England and Wales. Clinical guidelines are based on the best available evidence. Guidelines help healthcare professionals in their work, but they do not replace their knowledge and skills.'

The heading in the advertisement clearly related to information contained within a technology appraisal, as opposed to clinical guidelines and, as explained above, the technology appraisal was clearly referenced.

The complainant had also noted that the

advertisement did not refer to familial hypercholesterolemia. The main body of the advertisement did not mention this as this condition was not part of the scope of the NICE technology appraisal for ezetimibe. However, the prescribing information included the licensed indications for the product and stated, for instance, that Ezetrol was indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolemia who were not appropriately controlled with a statin alone. Further, the appropriate management of patients with this condition was covered in a separate guideline (CG71) identification and management of familial hypercholesterolaemia, which was not a feature of this advertisement.

In summary the companies did not believe that the advertisement was either misleading or incapable of substantiation and therefore neither in breach of Clause 7.2 nor 7.4.

PANEL RULING

The Panel noted that the headline to the advertisement stated 'New NICE technology appraisal recommends ezetimibe alone or in combination with initial statin therapy.' The cited reference was the NICE technology appraisal guidance 132 published in November 2007. The advertisement was published in September 2008. In May 2008 NICE had issued Clinical Guideline 67 on Lipid Modification. The advertisement at issue was clearly about lipid control and the Panel considered that a reference to something 'new' from NICE might be assumed by some readers to be the document issued four months earlier (the clinical guideline) and not the document issued ten months previously (the technology appraisal). Nonetheless the heading clearly referred to the technology appraisal and so in that regard the Panel considered that the advertisement was not misleading and no breach of Clause 7.2 was ruled.

The Panel noted that the technology appraisal guidance 132 (Ezetimibe for the treatment of primary (heterozygous – familial and non-familial) hypercholesterolaemia) was solely about ezetimibe and its place in therapy. The medicine was recommended for use either alone or in combination with initial statin therapy. It was noted, however, that, *inter alia*, a clinical guideline on lipid modification was under development and that the technology appraisal guidance should be read in the context of the relevant clinical guideline when available. The lipid modification clinical guideline was published in May 2008.

The lipid modification document examined the whole therapy area and the use of lipid modification therapy, not just the use of ezetimibe. The title page stated that the clinical guideline was concerned with 'Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease'. In a section looking at treatment pathways for primary and secondary prevention it was stated that one of the treatment choices for patients who could not tolerate statins for primary prevention was ezetimibe. Readers were referred to the NICE technology appraisal guidance 132 for the treatment of primary (heterozygous-familial and non familial) hypercholesterolaemia. The clinical guideline was silent upon the use of combination therapy of any kind.

The Panel noted the complainant's comments regarding the clinical guideline and that it gave a less significant place in treatment for ezetimibe in primary and secondary prevention than the technology appraisal. The two documents had to be considered together. The clinical guideline had not rendered the ezetimibe technology appraisal irrelevant. The advertisement at issue was about the use of Ezetrol not about the broad therapy area of lipid lowering. The Panel considered that it was true to state that, if and when ezetimibe was to be prescribed, NICE had recommended its use either alone or in combination with initial statin therapy. In that regard the Panel considered that the headline claim was not misleading as alleged and that it could be substantiated. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted that the main part of the advertisement did not refer to familial hypercholesterolaemia; the indications for ezetimibe were stated in the prescribing information ie primary (heterozygous familial and non-familial) hypercholesterolaemia, homozygous familial hypercholesterolaemia and homozygous sitosterolaemia. The NICE technology appraisal guidance referred to in the headline was about the use of ezetimibe for the treatment of primary- (heterozygous familial and non-familial) hypercholesterolaemia. The Panel considered that the prescribing information was adequate with regard to the stated use of ezetimibe and that the advertisement was not misleading in that regard. No breach of Clause 7.2 was ruled.

Complaint received 3 November 2008

Case completed 23 December 2008

PRIMARY CARE TRUST HEAD OF MEDICINES MANAGEMENT AND GP MEDICAL ADVISOR/GENERAL PRACTITIONER v PFIZER

Lipitor journal advertisement

The head of medicines management at a primary care trust and a GP medical advisor/general practitioner complained jointly about a journal advertisement for Lipitor (atorvastatin) placed by Pfizer.

The advertisement was headed 'New NICE [National Institute for Health and Clinical Excellence] lipid modification & Type 2 diabetes guidelines published' beneath which was the claim that 'New NICE guidelines recommend lowering cholesterol to <4mmol/L Total-cholesterol or <2mmol/L LDL-cholesterol to improve cardiovascular outcomes for patients with established CVD [cardiovascular disease] or Type 2 diabetes'. This was followed by claims that 'Economic modelling estimates that only 37% of patients with established CVD, with or without diabetes, achieve a Total-cholesterol <4mmol/L with simvastatin 40mg' and 'An estimated 82% of these patients would achieve a Total-cholesterol <4mmol/L with a simvastatin 40mg – Lipitor titration strategy'.

The complainants stated that the prominence of the heading that new NICE guidelines recommended lowering cholesterol to 4 and 2 was misleading as this only applied to NICE guidance for cholesterol management in secondary prevention in patients with established CVD or type 2 diabetes. Although this was implied, the way that the sentence was broken to fit around the prominent graphic of cholesterol levels of 4 and 2 was misleading and was deliberately designed to imply that the NICE guidance was a total cholesterol <4mmol/L and an LDL-cholesterol <2mmol/L for all patients. There was no reference to the NICE lipid modification recommendations in patients for primary prevention which was the vast majority of patients that required lipid modification therapy.

The second point implied that only 37% of patients with established CVD would achieve the recommended cholesterol targets with simvastatin, whereas 82% of patients would achieve the target with the Lipitor titration strategy. This claim was referenced to data on file. The complainants, however, were concerned that the data related to a study that had not been published or peer reviewed and was an economic profiling study, not a study done in actual patients but an implied benefit using cholesterol prevalence data from UK population

data and statin lowering efficacy data from a different study conducted in the USA. This data was not robust enough to support the claims made.

Lastly, the complainants alleged that the advertisement implied that Lipitor was endorsed by the NICE guideline on lipid modification which was incorrect. The NICE guideline stipulated that if a patient failed to reach target then simvastatin 80mg, or a medicine of similar efficacy and cost, should be used. As atorvastatin was six times the cost of simvastatin it could not satisfy the NICE recommendations as a medicine of similar efficacy and cost.

The detailed response from Pfizer is given below

The Panel considered that the combination of the heading and the claim that immediately followed made it clear that the advertisement referred to new NICE guidelines on lipid modification for patients with established CVD or type 2 diabetes. The Panel did not consider that the advertisement implied that NICE had recommended a total cholesterol of <4mmol/L and an LDL-cholesterol of <2mmol/L for all patients. It was acceptable for an advertisement to refer to a subset of patients ie in this case those with established CVD or type 2 diabetes, and not the vast majority of patients provided this was made clear. The Panel did not consider the advertisement was misleading as alleged and no breach of the Code was ruled.

The Panel was concerned about the claim relating to economic modelling estimates. However it was not a breach of the Code per se to cite 'data on file'. The Code required that claims were capable of substantiation. The Panel noted that the economic analysis used data from two sources. Firstly, the THIN database gave the baseline cholesterol levels. Secondly the lipid lowering efficacy data for each statin was based on the CURVES study. The Panel noted that the advertisement made clinical claims based on the economic modelling data. This was reinforced by the way the claims were presented in that '37%' and '82%' were in large bold type. The figures thus appeared to be proven absolutes. The reference to 'estimates' did not negate this impression. Further, the heading to the advertisement referred to clinical data. The Panel considered that given their context the claims at issue were misleading and not capable of

substantiation. Pfizer had not submitted clinical data to support the quoted percentages of patients achieving a total cholesterol of <4mmol/L. The Panel ruled breaches of the Code.

The Panel noted that the heading and first part of the advertisement referred to NICE guidelines targets and then in a different colour text referred to the lipid lowering efficacy of simvastatin and Lipitor. The claim 'Lipitor is an evidence-based choice when your patients with established CVD or Type 2 diabetes with CVD need intensive cholesterol-lowering for improved cardiovascular outcomes' did not refer to NICE. The context in which a claim appeared, however, was important; the two claims which headed the advertisement at issue referred to NICE guidelines. Nonetheless, on balance, the Panel did not consider that the advertisement implied that Lipitor was endorsed by the NICE guideline on lipid modification as alleged. The advertisement was thus not misleading in that regard and the Panel ruled no breach of the Code.

The head of medicines management at a primary care trust and a GP medical advisor/general practitioner complained jointly about a journal advertisement (ref LIP3055c) for Lipitor (atorvastatin) placed by Pfizer Limited in Guidelines in Practice, volume II, 7 July.

The advertisement in question was headed 'New NICE [National Institute for Health and Clinical Excellence] lipid modification & Type 2 diabetes guidelines published' beneath which was the claim that 'New NICE guidelines recommend lowering cholesterol to <4mmol/L Total-cholesterol or <2mmol/L LDL-cholesterol to improve cardiovascular outcomes for patients with established CVD [cardiovascular disease] or Type 2 diabetes'. This was followed by claims that 'Economic modelling estimates that only 37% of patients with established CVD, with or without diabetes, achieve a Total-cholesterol <4mmol/L with simvastatin 40mg' and 'An estimated 82% of these patients would achieve a Total-cholesterol <4mmol/L with a simvastatin 40mg – Lipitor titration strategy'.

COMPLAINT

The complainants alleged that the advertisement appeared to contravene Clauses 7.2, 7.3 and 7.4 of the Code.

The complainants stated that the prominence of the heading that new NICE guidelines recommended lowering cholesterol to 4 and 2 was misleading as this only applied to NICE guidance for cholesterol management in secondary prevention in patients with established CVD or type 2 diabetes. Although this was implied, the way that the sentence was broken to fit around the prominent graphic of cholesterol levels of 4 and 2 was misleading and was deliberately designed to imply that the NICE guidance was a total cholesterol <4mmol/L and an

LDL-cholesterol <2mmol/L for all patients. There was no reference to the NICE lipid modification recommendations in patients for primary prevention which was the vast majority of patients that required lipid modification therapy.

The second point implied that only 37% of patients with established CVD would achieve the recommended cholesterol targets with simvastatin, whereas 82% of patients would achieve the target with the Lipitor titration strategy. This claim was referenced to data on file. The complainants, however, were concerned that the data related to a study that had not been published or peer reviewed and was an economic profiling study, not a study in actual patients but an implied benefit using cholesterol prevalence data from UK population data and statin lowering efficacy data from a different study conducted in the USA. This data was not robust enough to support the claims in the advertisement.

Lastly, the complainants alleged that the advertisement implied that Lipitor was endorsed by the NICE guideline on lipid modification. This was incorrect, the NICE guideline stipulated that if a patient failed to reach target then simvastatin 80mg, or a medicine of similar efficacy and cost, should be used. As atorvastatin was six times the cost of simvastatin it could not satisfy the NICE recommendations as a medicine of similar efficacy and cost, therefore it was not recommended by the NICE guidelines on lipid modification.

RESPONSE

Pfizer stated that the advertisement aimed to raise awareness of the newly published NICE lipid modification and type 2 diabetes clinical guidelines with regard to the recommendation to achieve lower cholesterol levels of total cholesterol <4mmol/L in high risk patients with established CVD and type 2 diabetes.

Pfizer submitted that it had been explicit throughout the advertisement about the population of patients the recommendations were for ie patients with established CVD and those with type 2 diabetes. The sentence below the graphic of <4mmol/L total cholesterol or <2mmol/L LDL cholesterol referred to improving cardiovascular outcomes for patients with established CVD and type 2 diabetes. In addition, the advertisement referred throughout only to patients with established CVD and type 2 diabetes. For example, economic modelling estimates were presented for patients with established CVD, with or without diabetes. The boxed statement highlighted the role of Lipitor in reducing cholesterol in patients with established CVD or type 2 diabetes.

The objective of the advertisement was to raise awareness of recommended cholesterol levels in secondary prevention patients and type 2 diabetics. The NICE lipid modification clinical guidance did not

recommend a target level for total or LDL cholesterol for primary prevention and as such it would be inappropriate to refer to this population of patients in this advertisement which focused on the recommendations of lowering total cholesterol to <4mmol/L or LDL-cholesterol to <2mmol/L. In addition, it might be potentially misleading to include the primary prevention population in Lipitor advertising as NICE had explicitly recommended simvastatin 40mg (or a medicine of similar efficacy or cost) for the treatment of these patients and did not recommend intensifying lipid lowering therapy thereafter.

Finally, whilst Pfizer agreed that the vast majority of patients who required lipid modification therapy were primary prevention patients, it was entirely reasonable for advertising to focus on a specific population of patients and not the majority.

With regard to the complainants' concerns about the claims 'Economic modelling estimates that only 37% of patients with established CVD, with or without diabetes, achieve a total cholesterol <4mmol/L with simvastatin 40mg' and 'An estimated 82% of these patients would achieve a total cholesterol <4mmol/L with a simvastatin 40mg - Lipitor titration strategy', Pfizer submitted that these estimates were based on analysis obtained from the Titration Outcomes Cost-effectiveness Model (TOCEM). A description of the methodology underpinning this tool was provided.

Whilst Pfizer acknowledged that TOCEM had not been published, in response to a request from NICE this year, a working, fully executable version of this model was shared with NICE. Pfizer did not know what NICE had used the model for but had always ensured that it was fully transparent with all the cost-effectiveness models it developed and had always been prepared to answer any questions about the workings of the model.

It had been made explicitly clear in the advertisement that the claims referred to an economic analysis and therefore, were not misleading. Whilst the majority of statin clinical trials compared a fixed dose of a statin against another, in the real world, clinicians often utilised a range of statins and doses to lower cholesterol. At present, there was limited literature on the impact of different statin titration strategies on the attainment of post-treatment total cholesterol thresholds. TOCEM was an innovative model which attempted to simulate real-life cholesterol management in the UK and used inputs from both published clinical trial and observational data. The observational data used were the UK baseline cholesterol values from The Health Improvement Network (THIN) database which had been published in a peer-reviewed journal.

TOCEM utilised UK baseline cholesterol values from the THIN database, the results of which had been published in a peer-reviewed publication. In addition, Pfizer noted that cholesterol values from

its analysis had been adopted by NICE; the assumption of an average cholesterol level of 6.1mmol/L for non-diabetic CVD patients based on a distribution of patients taken from the THIN database was a key assumption underpinning the cost-effectiveness model within the NICE lipid modification clinical guideline.

Statin lowering efficacy data was obtained from the CURVES meta-analysis of statin trials, performed in the US and across Europe. Furthermore, the use of a large meta-analysis of clinical trials was recognised by NICE as level 1 evidence. The CURVES meta-analysis was chosen as a reference for statin lowering efficacy data because it was the largest meta-analysis of statin trials showing average total cholesterol reductions for individual statins and doses with associated p-values.

Pfizer did not agree that the advertisement implied that the NICE lipid modification guideline endorsed Lipitor, when NICE actually recommended that simvastatin 80mg (or a medicine of similar efficacy or cost) be used if a patient did not achieve the recommended cholesterol levels with simvastatin 40mg. The advertisement simply raised awareness of the new lower cholesterol levels recommended by NICE and went on to state how, by titrating up to Lipitor from simvastatin 40mg, more patients could achieve these levels. The final claim in the advertisement stated 'Lipitor is an evidence-based choice when your patients with established CVD or Type 2 diabetes with CVD need intensive cholesterol-lowering for improved cardiovascular outcomes'. This was to remind prescribers that Lipitor 20mg/40mg/80mg provided greater lipid lowering than simvastatin 40mg and had robust clinical data showing that it lowered cholesterol effectively to improve cardiovascular outcomes.

For the reasons outlined above, Pfizer denied breaches of Clauses 7.2, 7.3 and 7.4.

PANEL RULING

The Panel considered that the combination of the heading and the claim that immediately followed made it clear that the advertisement referred to new NICE guidelines on lipid modification for patients with established CVD or type 2 diabetes. The Panel did not consider that the advertisement implied that NICE had recommended a total cholesterol of <4mmol/L and an LDL-cholesterol of <2mmol/L for all patients. It was acceptable for an advertisement to refer to a subset of patients ie in this case those with established CVD or type 2 diabetes, and not the vast majority of patients provided this was made clear. The Panel did not consider the advertisement was misleading as alleged and no breach of Clause 7.2 was ruled.

The Panel was concerned about the claim relating to economic modelling estimates. However it was not a breach of the Code *per se* to cite 'data on

'file' in support of promotional claims. The Code required that claims were capable of substantiation. The Panel noted that the economic analysis used data from two sources. Firstly, the THIN database gave the baseline cholesterol levels. Secondly the lipid lowering efficacy data for each statin was based on the CURVES study. The Panel noted that the advertisement made clinical claims based on the economic modelling data. This was reinforced by the way the claims were presented in that '37%' and '82%' were in large bold type which stood out compared to the rest of the text. The figures thus appeared to be proven absolutes. The reference to 'estimates' did not negate this impression. Further, the heading to the advertisement referred to clinical data. The Panel considered that given their context the claims at issue were misleading and not capable of substantiation. Pfizer had not submitted clinical data to support the quoted percentages of patients achieving a total cholesterol of <4mmol/L. The Panel ruled breaches of Clauses 7.2, 7.3 and 7.4.

The Panel noted that the heading and first part of the advertisement referred to NICE guidelines targets and then in a different colour text referred to the lipid lowering efficacy of simvastatin and Lipitor. The claim 'Lipitor is an evidence-based choice when your patients with established CVD or Type 2 diabetes with CVD need intensive cholesterol-lowering for improved cardiovascular outcomes' did not refer to NICE. The context in which a claim appeared, however, was important; the two claims which headed the advertisement at issue referred to NICE guidelines. Nonetheless, on balance, the Panel did not consider that the advertisement implied that Lipitor was endorsed by the NICE guideline on lipid modification as alleged. The advertisement was thus not misleading in that regard and the Panel ruled no breach of Clause 7.2.

Case received	14 November 2008
Case completed	8 January 2009

PHARMACIST PRACTITIONER v SCHERING-PLOUGH

NeoClarityn journal advertisement

A pharmacist practitioner complained about an advertisement for NeoClarityn (desloratadine) placed in GP, 7 November, by Schering-Plough.

The advertisement was headed 'Triple stopping power for allergic rhinitis' beneath which was an illustration of three goal keepers in a goal mouth. On the front of the goal keepers' shirts were the words 'anti-histaminic', 'anti-allergic' and 'anti-inflammatory' respectively.

The complainant considered that the claim that desloratadine was anti-inflammatory might be accurate for *in vitro* studies but to claim that it had clinically relevant anti-inflammatory actions was contradicted by the summary of product characteristics (SPC). The complainant alleged that the advertisement was inaccurate and therefore misleading.

The detailed response from Schering-Plough is given below.

The Panel noted that NeoClarityn was indicated for the relief of symptoms associated with allergic rhinitis and urticaria. The SPC stated that desloratadine had demonstrated anti-allergic properties from *in vitro* studies including inhibition of the release of pro-inflammatory cytokines. The clinical relevance of these observations remained to be confirmed.

The Panel noted that there was some data (Bachert and Reinartz *et al*) to suggest that desloratadine might have an anti-inflammatory effect. However Bachert had reported only the preliminary results from a study conducted by others (Marshall *et al* 2002), and Reinartz *et al* was unable to show that airway mucosal inflammation was altered by one week's treatment.

The Panel considered that the impression from the advertisement was that NeoClarityn was authorized for use as an antihistamine, an anti-allergic or an anti-inflammatory and that clinical data supported each element. This was not so with regard to the anti-inflammatory action as acknowledged by Schering-Plough. The advertisement was inconsistent with the NeoClarityn SPC and was misleading as alleged. Breaches of the Code were ruled.

A pharmacist practitioner complained about an advertisement (ref NCL/08-579) for NeoClarityn (desloratadine) placed in GP, 7 November, by Schering-Plough Ltd.

The advertisement was headed 'Triple stopping

power for allergic rhinitis' beneath which was an illustration of three goal keepers in a goal mouth. On the front of the goal keepers' shirts were the words 'anti-histaminic', 'anti-allergic' and 'anti-inflammatory' respectively.

NeoClarityn was indicated for the relief of symptoms associated with allergic rhinitis and urticaria.

COMPLAINT

The complainant noted that the advertisement cited three references; one was the current summary of product characteristics (SPC) which stated:

'Desloratadine has demonstrated antiallergic products from *in vitro* studies. These include inhibiting the release of proinflammatory cytokines such as IL-4, IL-6, IL-8, and IL-13 from human mast cells/basophils, as well as inhibition of the expression of the adhesion molecule P-selectin on endothelial cells. The clinical relevance of these observations remains to be confirmed.'

The complainant considered that the claim that desloratadine was anti-inflammatory might be accurate for *in vitro* studies but to claim that it had clinically relevant anti-inflammatory actions was contradicted by the SPC.

The complainant alleged that the advertisement was inaccurate and therefore misleading.

When writing to Schering-Plough the Authority asked it to respond in relation to Clauses 3.2 and 7.2 of the Code.

RESPONSE

Schering-Plough stated that the advertisement listed three pharmacodynamic properties of desloratadine that were referred to in the SPC ie anti-allergenic, anti-histaminic and anti-inflammatory. The advertisement referred readers to three sources of information; the SPC, Marshall (2000) and Molet *et al* (1997). The complainant unfortunately considered that the inclusion of the phrase 'anti-inflammatory' did not reflect the data contained in the SPC and was therefore inaccurate and misleading.

Schering-Plough submitted that the current available data supported the use of the phrase 'anti-inflammatory' in the advertisement. Desloratadine

was among the newest anti-allergy products, developed from second-generation anti-histamines. Its anti-inflammatory activity was well recognised in scientific literature, both *in vitro* and *in vivo*. For instance, Marshall commented 'the high therapeutic index for antiallergenic and anti-inflammatory effects of newer agents, such as desloratadine, offers promise for improved therapeutic and perhaps even prophylactic options'. Geha and Meltzer (2001) stated 'Desloratadine is a new, selective, H₁-receptor antagonist that also has anti-inflammatory activity'.

Schering-Plough noted the requirements of Clause 7.2, specifically that *in vitro* data might only be extrapolated to the clinical situation if there was data to show that it was of direct relevance and significance. Geha and Meltzer considered that observations from the *in vitro* studies were relevant to clinical use. 'Regardless, the mechanism by which desloratadine exerted these anti-inflammatory effects was independent of H₁-receptor antagonism, and it was reasonable to consider the observations from these studies to be relevant to clinical use'.

To further substantiate the clinical relevance of *in vitro* data, *in vivo* studies in subjects with allergic rhinitis confirmed the systemic anti-inflammatory effect of desloratadine. Bachert (2002) observed decreased expression of IL-4, IL-5 and IL-10 in patients treated with desloratadine compared with those treated with placebo. Also, Reinartz *et al* (2005) concluded that desloratadine reduced systemic allergic inflammation following nasal provocation in allergic rhinitis and asthma patients.

Direct evidence for clinical relevance was derived from clinical studies. Clinically, the late inflammatory response was associated with symptoms of nasal obstruction and increased mucus production. In two different clinical trials, patients with allergic rhinitis treated with desloratadine had greater reduction in nasal obstruction and nasal congestion compared with those treated with placebo, confirming the anti-inflammatory component.

Therefore, based on the specific *in vitro*, *in vivo* and clinical data for desloratadine discussed above,

Schering-Plough believed that it could substantiate a claim that the product had anti-inflammatory properties. However, it noted the complainant's concerns that the advertisement did not include a clear explanation of these data. Therefore, working in the spirit of the Code, Schering-Plough had withdrawn the advertisement. Any future use of the claim would include clear explanation of the nature of the *in vitro* data and also the *in vivo* and clinical data to enable readers to make an informed opinion.

PANEL RULING

The Panel noted that NeoClarityn was indicated for the relief of symptoms associated with allergic rhinitis and urticaria. Section 5.1 of the SPC stated that desloratadine had demonstrated anti-allergic properties from *in vitro* studies including inhibition of the release of pro-inflammatory cytokines. The clinical relevance of these observations remained to be confirmed.

The Panel noted that there was some data (Bachert and Reinartz *et al*) to suggest that desloratadine might have an anti-inflammatory effect. However Bachert had reported only the preliminary results from a study conducted by others (Marshall *et al* 2002), and Reinartz *et al* was unable to show that airway mucosal inflammation was altered by one week's treatment.

The Panel considered that the impression from the advertisement was that NeoClarityn was authorized for use as an antihistamine, an anti-allergic or as an anti-inflammatory and that clinical data supported each element. This was not so with regard to the anti-inflammatory action as acknowledged by Schering-Plough. The Panel considered that in that regard the advertisement was inconsistent with the particulars listed in the NeoClarityn SPC. A breach of Clause 3.2 was ruled. The advertisement was misleading as alleged and thus the Panel ruled a breach of Clause 7.2.

Complaint received 17 November 2008

Case completed 5 January 2009

PHARMACIST PRACTITIONER v ASTRazeneca

Crestor journal advertisement

A pharmacist practitioner complained about an advertisement for Crestor (rosuvastatin) issued by AstraZeneca in GP, 7 November. The advertisement had a picture of a smaller than normal dartboard with the caption, 'Finding cholesterol targets harder to hit?'.

The complainant stated that the National Institute for Health and Clinical Excellence (NICE) guidance relating to lipid modification (Clinical Guidance (CG) 67) was published in May. The guidance recommended no target for patients being treated for primary prevention. Those being treated for secondary prevention were recommended for treatment with simvastatin 40mg. The audit level targets remained at 5mmol/L for total cholesterol and 3mmol/L for LDL cholesterol. These targets had not changed although the guidance recommended aspirational levels of 4mmol/L and 2mmol/L respectively after consideration of risks and benefits. Additionally, the guidance recommended using simvastatin 80mg or a statin of 'similar efficacy and cost'.

The complainant alleged that the advertisement was misleading in that it implied that targets had recently been reduced when in fact they had not. The advertisement also failed to mention the first line recommendations made by NICE.

The detailed response from AstraZeneca is given below.

The Panel noted that the advertisement featured a picture of a very small dartboard in the middle of an outline of a normal sized scoreboard. The dartboard had been shown in a much smaller scale than everything else around it. The only text in the advertisement, apart from the prescribing information and other required information was the product logo in the bottom right-hand corner together with the strap-line 'Finding cholesterol targets harder to hit?'.

The Panel noted that Crestor was indicated for the management of primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (eg exercise, weight reduction) was inadequate. Crestor could also be used for homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (eg LDL apheresis) if such treatments were not appropriate.

The Panel noted AstraZeneca's submission about the various guidance documents issued by NICE

since May 2008; *inter alia*, new cholesterol goals had been set for patients with diabetes and a new target had been set for patients with familial hypercholesterolaemia. NICE recommended high intensity statins in some patients. In the Panel's view there was a difference between overall targets which might be applicable to a patient population compared with a cholesterol target for a specific patient in a high risk group. The complainant's concerns appeared to be based only on the NICE clinical guideline 67 – Lipid Modification.

On balance, the Panel considered that the strapline 'Finding cholesterol targets harder to hit?' with the small dartboard might imply that targets had recently been reduced. However the advertisement might also be read as implying that it was more difficult to hit cholesterol targets generally. Lipid targets had now been set for a broad range of patients by a range of organisations. The strapline asked a question, it did not make a statement. If the reader's answer to the question was 'yes' then perhaps Crestor might be appropriate for some patients. The Panel did not consider that the strapline was misleading as alleged. No breach of the Code was ruled.

The Panel noted that the advertisement did not mention NICE at all. Thus it did not consider that the failure to mention the first line recommendations made by NICE was misleading. No breach was ruled.

A pharmacist practitioner complained about an advertisement for Crestor (rosuvastatin) placed by AstraZeneca UK Limited in GP, 7 November.

COMPLAINT

The complainant stated that the advertisement had a picture of a smaller than normal dartboard with the caption, 'Finding cholesterol targets harder to hit?'.

The National Institute for Health and Clinical Excellence (NICE) guidance relating to lipid modification (Clinical Guidance (CG) 67) was published in May and this document must be recognised as defining the national targets for cholesterol levels in England and Wales.

The guidance recommended no target for patients being treated for primary prevention. Those being treated for secondary prevention were recommended for treatment with simvastatin 40mg. The audit level targets remained at 5mmol/L for total cholesterol and 3mmol/L for LDL cholesterol.

These targets had not changed although the guidance recommended aspirational levels of 4mmol/L and 2mmol/L respectively after consideration of risks and benefits. Additionally, the guidance recommended using simvastatin 80mg or a statin of 'similar efficacy and cost'.

The complainant considered that the advertisement was misleading in that it implied that targets had recently been reduced when in fact they had not. The advertisement also failed to mention the first line recommendations made by NICE.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clause 7.2 of the Code.

RESPONSE

AstraZeneca stated that cholesterol management applied to a broad spectrum of patients; this included patients with dyslipidaemia, familial hypercholesterolaemia, diabetes and secondary prevention after a cardiovascular event. Since May 2008 there had been numerous guidelines advocating lower total cholesterol and LDL cholesterol targets in order to treat these high-risk groups (ie NICE guidance for secondary prevention (CG67), diabetes (CG66) and familial hypercholesterolaemia patients (CG71)). The recommendations in these NICE guidelines had changed from previous iterations; therefore the advertisement was simply asking whether prescribers were achieving the required cholesterol levels for their patients.

The complainant recognised the NICE lipid modification guidance (CG67, May 2008), but failed to recognise the recent NICE guidance for diabetes and familial hypercholesterolaemia and other local initiatives throughout the UK.

As stated in the NICE diabetes guidance (CG66, May 2008):

'Consider intensifying cholesterol-lowering therapy (with a more effective statin or ezetimibe in line with NICE guidance) if there is existing or newly diagnosed cardiovascular disease, or if there is an increased albumin excretion rate, to achieve a total cholesterol level below 4.0mmol/litre (and HDL cholesterol not exceeding 1.4mmol/litre) or an LDL cholesterol level below 2.0mmol/litre.'

Thus new cholesterol goals had been set by NICE for patients with diabetes.

In August 2008 NICE issued its first guideline for patients with familial hypercholesterolaemia (CG71) where it stated for adult patients:

'Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline.'

Thus a new target for the management of familial hypercholesterolaemia had been advocated by NICE.

The lipid modification guidance (CG67) referred to by the complainant, stated that in secondary prevention patients:

'People with acute coronary syndrome should be treated with a higher intensity statin. Any decision to offer a higher intensity statin should take into account the patient's informed preference, comorbidities, multiple drug therapy, and the benefits and risks of treatment.'

The NICE lipid modification guidance, familial hypercholesterolaemia guidance and the diabetes guidance all defined a 'high intensity statin' as any statin that had higher LDL cholesterol lowering efficacy than simvastatin 40mg, eg the familial hypercholesterolaemia guidance stated:

'High intensity statin: statins are classified as high intensity if they produce greater LDL-cholesterol reductions than simvastatin 40mg (e.g. simvastatin 80mg and appropriate doses of atorvastatin and rosuvastatin).'

The NICE lipid modification guidance also stated:

'In people taking statins for secondary prevention, consider increasing to simvastatin 80mg or a drug of similar efficacy and acquisition cost if a total cholesterol of less than 4mmol/litre or an LDL cholesterol of less than 2mmol/litre is not attained. Any decision to offer a higher intensity statin should take into account informed preference, comorbidities, multiple drug therapy, and the benefit and risks of treatment.'

The cholesterol lowering effect of various statins at different doses were listed in the lipid modification guidance, which showed that all doses of rosuvastatin provided greater total and LDL cholesterol lowering than simvastatin 40mg.

However, AstraZeneca recognised that the lipid guidance also stated:

'An "audit" level of total cholesterol of 5mmol/litre should be used to assess progress in populations or groups of people with CVD, in recognition that more than a half of patients will not achieve a total cholesterol of less than 4mmol/litre or an LDL cholesterol of less than 2mmol/litre.'

This was just an audit standard and not a treatment goal for an individual patient. NICE clearly recognised that not all patients would be able to achieve a target for total cholesterol <4mmol/L and LDL cholesterol <2mmol/L and therefore a minimum audit level of total cholesterol <5mmol/L and LDL cholesterol <3mmol/L could be used when assessing cholesterol treatment at a population level.

Apart from recent NICE guidance for England and Wales there was also additional evidence of cholesterol targets changing at a national and local level. For example in Northern Ireland (from the Department of Health, Social Services and Public Safety) the national guidance was to 'aim for a total cholesterol of <4mmol/L, LDL cholesterol of <2mmol/L and an HDL cholesterol >1mmol/L'.

On a local level the Essex Cardiac Network which covered five PCTs had issued guidance since the NICE guidance was issued (September 2008) to treat to a total cholesterol of <4mmol/L, LDL cholesterol <2mmol/L, triglycerides <1.7mmol/L and HDL cholesterol > 1mmol/L for men and >1.3mmol/L for women.

The above examples demonstrated that cholesterol management in a broad range of patients was becoming more challenging due to changes in local and national targets and therefore AstraZeneca did not consider that the advertisement at issue was misleading and in breach of Clause 7.2.

AstraZeneca considered that the wording 'Finding cholesterol targets harder to hit?' gave the reader the option to decide for themselves whether this question was important to them in the management of their patients. If indeed the reader/prescriber had not found their patients' cholesterol targets harder to hit then this advertisement might not apply to them.

AstraZeneca did not therefore accept that there had been a breach of Clause 7.2.

PANEL RULING

The Panel noted that the advertisement featured a picture of a very small dartboard in the middle of an outline of a normal sized scoreboard. The diameter of the dartboard appeared to be less than the length of some darts which lay below it. The dartboard had thus been shown in a much smaller scale than everything else around it. The only text in the advertisement, apart from the prescribing information and other required information was the product logo in the bottom right-hand corner together with the strap-line 'Finding cholesterol targets harder to hit?'.

The Panel noted that Crestor was indicated for the management of primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (eg exercise, weight reduction) was inadequate. Crestor could also be used for homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (eg LDL apheresis) if such treatments were not appropriate.

The Panel noted AstraZeneca's submission about the various guidance documents issued by NICE since May 2008; *inter alia*, new cholesterol goals had been set for patients with diabetes and a new target had been set for patients with familial hypercholesterolaemia. NICE recommended high intensity statins in some patients. In the Panel's view there was a difference between overall targets which might be applicable to a patient population compared with a cholesterol target for a specific patient in a high risk group. The complainant's concerns appeared to be based only on the NICE clinical guideline 67 – Lipid Modification.

On balance, the Panel considered that the strapline 'Finding cholesterol targets harder to hit?' with the small dartboard might imply that targets had recently been reduced. However the advertisement might also be read as implying that it was more difficult to hit cholesterol targets generally. Lipid targets had now been set for a broad range of patients by a range of organisations. The strapline asked a question, it did not make a statement. If the reader's answer to the question was 'yes' then perhaps Crestor might be appropriate for some patients. The Panel did not consider that the strapline was misleading as alleged. No breach of Clause 7.2 was ruled.

The Panel noted that the advertisement did not mention NICE at all. Thus it did not consider that the failure to mention the first line recommendations made by NICE was misleading. No breach of Clause 7.2 was ruled.

Complaint received 17 November 2008

Case completed 6 January 2009

CODE OF PRACTICE REVIEW – FEBRUARY 2009

Cases in which a breach of the Code was ruled are indexed in **bold type**.

2158/8/08	Pharmacist Practitioner v Sanofi-Aventis	Provision of promotional aids for Acomplia	No breach	Appeal by complainant	Page 3
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2172/10/08	Boehringer Ingelheim v Bayer Schering Pharma	Promotion of Xarelto	Breach Clause 2 Two breaches Clause 3.1 Two breaches Clause 7.2 Breaches Clauses 7.3, 8.1, 9.10 and 18.2	No appeal	Page 39
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2174/10/08	Anonymous v Merck Serono	Alleged inappropriate hospitality	No breach	No appeal	Page 50
2175/10/08	Anonymous General Practitioner v ProStrakan	Osteoporosis audit service	Two breaches Clause 9.1	No appeal	Page 54
2176/10/08	Nurse v Schering-Plough	Alleged breach of confidentiality	No breach	No appeal	Page 61
2178/10/08	Anonymous v GlaxoSmithKline	Patient outcomes and information service	No breach	No appeal	Page 65
2179/10/08	Pharmacist Head of Prescribing Team v Pfizer	Lipitor mailing	Breach Clause 7.2	No appeal	Page 70
2180/11/08 and 2181/11/08	Associate Director Pharmacy policy & Prescribing v Merck Sharp & Dohme and Schering-Plough	Ezetrol journal advertisement	No breach	No appeal	Page 72

2184/11/08	Primary Care Trust Head of Medicines Management and GP Medical Advisor/ General Practitioner v Pfizer	Lipitor journal advertisement	Breaches 7.2, 7.3 and 7.4	Clauses No appeal	Page 75
2185/11/08	Pharmacist Practitioner v Schering-Plough	NeoClarityn journal advertisement	Breaches 3.2 and 7.2	Clauses No appeal	Page 79
2186/11/08	Pharmacist Practitioner v AstraZeneca	Crestor journal advertisement	No breach	No appeal	Page 81

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, over sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about prescription only medicines made available to the public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the sponsorship of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

It also covers:

- the provision of information to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations
- the use of consultants
- non-interventional studies of marketed medicines
- grants and donations to institutions.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines, or the provision of information to the public, should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY

telephone 020 7747 8880
facsimile 020 7747 8881
by email to: complaints@pmcpa.org.uk.