PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 55 FEBRUARY 2007

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

Complaints in 2006 up on 2005

In 2006 the Authority received 134 complaints as compared with 101 in 2005. There were 119 complaints in 2004, 131 in 2003 and 127 in 2002.

The average number of complaints received each year since the Authority was established at the beginning of 1993 is 124, the numbers in individual years ranging from 92 in 1993 to 145 in both 1994 and 1997 without any perceptible reason for the variations seen.

There were 128 cases to be considered in 2006, as compared with 107 in 2005. The number of cases usually differs from the number of complaints because some complaints involve more than one company and because some complaints do not become cases at all, usually because no *prima facie* case is established.

The number of complaints from health professionals in 2006 exceeded the number from pharmaceutical companies. There were 57 from health professionals and 23 from pharmaceutical companies (both members and non-members of the ABPI). Complaints made by pharmaceutical companies are generally more complex than those from outside the industry, usually raising a number of issues.

Three complaints were made by members of the public, five by pharmaceutical company employees and two by anonymous employees. There were thirteen other anonymous complaints and four complaints were made by organisations.

The remaining 27 complaints were nominally made by the Director and arose from media criticism, other complaints, voluntary admissions by companies, scrutiny and alleged breaches of undertaking.

Sponsorship to attend meetings

Companies are reminded that the sponsorship of health professionals to attend meetings is subject to the Code (Clause 19 refers). Sponsorship to attend meetings at venues outside the UK is acceptable in appropriate circumstances. In particular, the level of the hospitality to be provided and the nature of the venue are among the factors to be considered.

Problems can arise for companies with company-sponsored events held outside the UK, particularly those which have been organised by a part of the company other than that which operates in the UK, but to which, from a corporate perspective, the UK company is expected to sponsor UK health professionals. Companies must ensure that their international/European colleagues are aware of the requirements of the Code in this regard. Before sponsoring attendance at such meetings UK companies must ensure that all of the arrangements for the UK health professionals to attend comply with the Code.

Representatives' briefing material

When a complaint is received about how a representative promoted a product the Authority may request a copy of the relevant briefing material. Briefing material must comply with the appropriate requirements of the Code and must be certified. It must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The detailed briefing material referred to in the Code consists of both the training material used to instruct representatives about a medicine and the instructions given to them as to how the product should be promoted.

Companies are reminded that briefing material can come from a number of sources including, *inter alia,* the marketing, training and sales departments. Even memoranda written by field managers to their representatives could, according to content, be viewed as briefing material. All briefing material, whatever its source, is subject to the Code and must be certified before use.

Welcome Julie

The Authority has welcomed Mrs Julie Gadsby to its staff. Julie is the Personal Assistant to the Director, Mrs Heather Simmonds, and her responsibilities include the organisation of the Authority's seminars on the Code of Practice. Her telephone number is 020 7747 1443 and her email address is jgadsby@pmcpa.org.uk.

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:

Friday, 22 June

Friday, 14 September

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

For further information regarding any of the above, please contact Julie Gadsby for details (020 7747 1443 or email jgadsby@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 8883 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.

General Medical Council

The General Medical Council (GMC) has updated its core piece of guidance to doctors and a new version 'Good Medical Practice (2006)' took effect on 13 November. One of the paragraphs dealing with conflicts of interest, which is currently cited in the supplementary information to Clauses 15.3, 18.1 and 19.1 of the Code, has been expanded slightly; it now reads 'You must act in your patients' best interests when making referrals and when providing or arranging treatment or care. You must not ask for or accept any inducement, gift or hospitality which may affect or be seen to affect the way you prescribe for, treat or refer patients. You must not offer such inducements to colleagues'.

Full details of the new guidance can be found at www.gmc-uk.org.

CASE AUTH/1855/6/06

NOVARTIS v ROCHE

CellCept booklet

Novartis complained about a CellCept (mycophenolate mofetil) booklet entitled 'Are you concerned about GI [gastrointestinal] complications after transplantation?' issued by Roche. CellCept was indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogenic, renal, cardiac or hepatic transplants. Novartis supplied Myfortic (enteric coated mycophenolate sodium) which was also used in combination with ciclosporin and corticosteroids but only for the prophylaxis of acute transplant rejection in adults receiving allogenic renal transplants. Novartis alleged the booklet misrepresented the role of immunosuppression, specifically CellCept, in the aetiology of GI complications following transplantation and was inconsistent with the CellCept summary of product characteristics (SPC).

Page 1 was headed 'GI complications in transplantation'. In a list of causes of GI adverse events infections was at the top and drug-induced effects, for example antibiotics and immunosuppressants, was at the bottom. Novartis believed this oversimplified the aetiology of GI adverse events to minimise the association with CellCept. In the context of a CellCept promotional piece, and in view of the prominence of GI side effects in the CellCept SPC, immunosuppression (if not specifically CellCept) should be listed first in any ranking of causes for GI side effects after transplantation; both because it was directly toxic to the GI tract and because it was a potent immunosuppressant that increased the risk of infections which might be associated with GI symptoms.

The Panel noted from the CellCept SPC that treatment should be initiated and maintained by appropriately qualified transplant specialists and that the principal adverse reactions associated with therapy included diarrhoea, leucopenia, sepsis and vomiting. The SPC also stated that all transplant patients were at increased risk of opportunistic infections; the risk increased with total immunosuppressive load. The most common infections in patients followed for at least one year were candida mucocutaneous, CMV viraemia/syndrome and Herpes simplex. With regard to GI adverse reactions, vomiting, abdominal pain, diarrhoea and nausea were listed as very common (≥1/10) and GI haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence and eructation were listed as common (≥ 1/100 to < 1/10).

The Panel noted that on the page headed 'GI complications in transplantation', specific mention was made regarding GI adverse events with CellCept. The page stated that 'The use of CellCept has led to significant reductions in graft rejection and improved long-term graft survival and function, but GI effects are still a concern with immunosupression'. Drug-induced effects were included on the list of causes of GI adverse events. The list did not give any indication of the incidence or ranking of the importance of infection, surgery, concomitant diseases or drugs in causing GI complications. The Panel noted that Rubin (2001) stated that it was often very difficult to distinguish between infection-related and immunosuppression-related GI complications after transplantation. The causes might differ depending upon the time post-transplant and this time line was helpful in determining whether a GI complication was likely to be related to infection rather than a specific effect of an immunosuppressant medicine.

The Panel did not accept that the list oversimplified the aetiology of GI adverse events. The booklet was aimed at a specialised audience. No breach of the Code was ruled.

Page 2 was sub headed 'Determining the probable cause can prove a prudent course of action' and included two quotations: 'Inappropriate dose reduction of an immunosuppressive agent that may not be the cause of the diarrhoea may result in an unnecessarily increased risk of acute rejection, the long-term impact of which is far more detrimental to patient or graft survival.' (Pescovitz *et al* 2001) and 'As infections very often have GI symptoms, it is important to rule out infection before looking to the immunosuppressive drug regimen as the cause of a patient's GI problem.' (Rubin 2001).

Novartis alleged that these quotations suggested that intervention to reduce GI side effects during Cellcept therapy should be delayed until GI symptoms had been investigated and implied that the true cause was frequently independent of the dose of immunosuppression given. These views were not consistent with the CellCept SPC. In addition, it was not made clear that the quotations represented opinions expressed in a journal supplement which had not been peer-reviewed rather than the evidence based conclusion of a study.

The Panel did not consider that the page was inconsistent with the CellCept SPC as alleged. The CellCept SPC listed GI adverse events as well as generally linking immunosuppression to infections. The specialist audience would be well aware of the difficulties with immunosuppression treatment. It was a matter for the specialists to decide whether to lower the dose of CellCept and when this should happen. The Panel did not accept that the page implied that the true cause of GI complications was frequently independent of the dose of immunosupressant used. In the Panel's view the main message of the page was summed up in the sub-heading 'Determining the probable cause can prove to be a prudent course of action'.

The Panel did not consider that the Code required promotional material to indicate that a quotation had been taken from a source that had not been peer-reviewed as alleged. The Code required quotations to be factual and accurate and not misleading. The source needed to be cited. The Panel ruled that on the evidence before it there was no breach of the Code.

Page 3 was sub headed 'The proven benefit of excluding infection' and presented data from Maes *et al* (2003) on 26 renal transplant patients on an

immunosuppressive regime which included CellCept. An infectious cause of diarrhoea was demonstrated in approximately 60% (n=13). A graph showed that of those thirteen patients 92% (n=12) had diarrhoea primarily treated with antimicrobial agents; in the remaining patient, with a concomitant malignant disorder, immunosuppressant therapy was stopped. The page concluded that 'Diarrhoea was successfully treated with antimicrobial agents without the need for permanent reduction or cessation of immunosuppressant'.

Novartis alleged that the strong claim of the 'proven' benefit of excluding infection was not supported by the data presented. Half of the 26 patients with diarrhoea, selected as a subset of 765 patients, had an infectious cause of their diarrhoea. This was clearly not a 'proven benefit', particularly when one considered that CellCept itself predisposed to infection through immunosuppression. Furthermore, the use of a graph with an impressive 92% graphic created a misleading impression of robust support for the claim.

The data presented related specifically to persistent afebrile diarrhoea but the headings were 'Managing GI adverse events' and 'The proven benefit of excluding infection'. Diarrhoea was only one of the GI adverse events listed in the CellCept SPC and no evidence was supplied for the benefit of excluding infection in the remainder.

The Panel noted that the graph on the page headed 'Managing GI adverse events' showed that 92% of patients had diarrhoea treated primarily with antimicrobial agents. A sub-heading read 'The proven benefit of excluding infection'. The Panel considered that at first glance the page seemed to suggest that in 92% of patients with GI adverse events, diarrhoea could be controlled with antimicrobials without the need to reduce the dose of immunosuppressant. This was not the case. The 92% related to the subset of patients with persistent afebrile diarrhoea in whom an infectious cause was found ie 13 patients. In the other patients in whom no infection was determined, immunosuppressive therapy was either reduced or stopped. Thus in an original group of 26 patients with afebrile diarrhoea, an infectious cause was demonstrated in 13, only 12 of whom were successfully treated with antibiotics ie <50% (12/26) as opposed to the 92% (12/13) depicted in the graph. The Panel considered that the page was misleading in this regard. The Panel also considered that it was misleading for a page headed 'Managing GI adverse events' to focus only on data in patients with persistent afebrile diarrhoea.

The graph presented the data accurately but in the Panel's view was not presented in such a way as to give a clear, fair, balanced view of the data. It was visually misleading. A breach of the Code was ruled. The Panel did not consider that the page failed to maintain a high standard.

Novartis alleged that pages 4 and 5, headed 'Managing GI adverse events' and 'Managing infectious diarrhoea' contributed to the impression that infection was the most important cause of GI upset and that it was independent of immunosuppression (Cellcept). The treatment algorithm suggested that immunosuppression should only be considered a cause for GI upset once infection had been excluded.

The Panel did not agree with Novartis' submission. The subheading implied that it was important to distinguish between infection-related and immunosuppression-related GI complications. In the Panel's view the pages encouraged a pragmatic approach ie that the cause of diarrhoea should be established before any treatment changes were introduced. The Panel did not consider that the pages were misleading and thus ruled no breach of the Code.

Page 7 'Managing non-infectious diarrhoea', referred to 10 patients of the 23 patients with afebrile diarrhoea that did not have an infectious cause and were presumed to have drug-induced diarrhoea (Maes *et al*). This was followed by 'All immunosuppressant regimens are associated with diarrhoea to a greater or lesser extent'. The frequency of study-reported diarrhoea post transplantation was given in a table.

Novartis stated that in an attempt to create a perception that the licensed use of CellCept was no more associated with GI adverse events than other immunosuppressants, GI adverse event rates seen with a number of alternative regimens were presented under the heading 'Frequency of study-reported diarrhoea post transplantation'. However, the combination of tacrolimus and CellCept was not licensed and the use of ciclosporin and sirolimus in combination beyond three months (as per the reference cited) was specifically contraindicated in the sirolimus SPC, making this another unlicensed safety claim.

The Panel noted that the combination of CellCept and tacrolimus was not mentioned in the therapeutic indications, Section 4.1, of the CellCept SPC. Mention was made in Section 4.5 interactions. The Panel did not consider that in the context of the table it was unreasonable to include details of the frequency of diarrhoea with this combination. Ciclosporin and sirolimus were licensed for use for 3 months. The Panel did not consider in the context of the page at issue that the information about the frequency of diarrhoea with regard to CellCept and tacrolimus and ciclosporin and sirolimus were unlicensed safely claims as alleged. No breach of the Code was ruled although the Panel considered that the information could have been better presented to make the limitations clear.

Novartis alleged that page 8 of the booklet headed 'Managing non-infectious diarrhoea' and sub headed 'Is there a role for enteric-coated mycopenolate sodium (EC-MPS) [Myfortic] in reducing GI complications?', disparaged its product, Myfortic. It presented a hypothesis based on a single bioavailability study that compared oral and IV administration of CellCept (ie a study that did not contain Myfortic. The hypothesis, which relied on the faulty premise of a single potential mechanism (topical effect), was used to support the statement 'As such, it is not surprising that the

enteric coat of MPS has no impact on GI complications'. It ignored alternative potential mechanisms, such as pharmacokinetic differences between the products.

The statement 'EC-MPS has no advantage on tolerability over CellCept and no proven role in patients failing to tolerate CellCept', was referenced to a letter of opinion, written by a single clinician and in French, and was not an evidence based conclusion. Data comparing the rate of diarrhoea with CellCept and Myfortic was taken from a study which excluded patients unable to tolerate CellCept and as such provided little insight into the relative tolerability of the two agents. The statement also ignored the fact that the exploration of potential GI differences between the products remained the subject of a study.

The Panel noted that Salvadori *et al* (2003) compared CellCept with Myfortic and concluded that the products were therapeutically equivalent with a comparable safety profile. Within 12 months 15% of Myfortic and 19.5% of CellCept patients required dose changes for GI adverse events (p=ns). The study was not designed to statistically detect differences between treatment groups in terms of GI tolerability. The claim that [Myfortic] had no impact on GI complications was a strong one. The Panel noted that although the claim '[Myfortic] has no advantage on tolerability over CellCept and no proven role in patients failing to tolerate CellCept' was referenced to a single author, it appeared to be a quotation in that paper from a larger body, it was thus not just the opinion of a single clinician. Novartis had not submitted data to support its complaint although a study was ongoing.

The comparison of rates of diarrhoea were from Budde *et al* (2003). The discussion noted that patients entered into the study were receiving and therefore tolerating [CellCept] at a dose of 2000mg which might introduce a bias. The Panel considered that the page had not put this data in context. It was inappropriate to follow the subheading 'Is there a role for enteric coated mycophenolate sodium (EC-MPS) in reducing GI complications' with data referring only to CellCept.

The Panel noted that according to the SPCs for CellCept and Myfortic, diarrhoea was a very common side effect with both (≥ 10%). However the other very common GI side effects of CellCept (vomiting, abdominal pain and nausea) only occurred commonly (≥ 1% and <10%) with Myfortic. Similarly some of the commonly occurring GI disorders with CellCept (eructation, ileus, oesophagitis, gastrointestinal haemorrhage) were uncommon (≥ 0.1% and <1%) with Myfortic. Thus, although both products were associated with a number of similar GI disorders there seemed to be a lessening of effect with Myfortic.

The Panel again noted that subheadings referred to GI complications as a whole whereas some of the data presented referred specifically to diarrhoea. On balance the Panel considered that the page disparaged Myfortic and a breach of the Code was ruled. This ruling was appealed by Roche.

The Appeal Board was concerned about the content and layout of the page at issue. It was inappropriate to follow the subheading 'Is there a role for enteric coated mycophenolate sodium (EC-MPS) in reducing GI complications' with data referring only to CellCept. The Appeal Board considered that the claim '… it is not surprising that the enteric coat of MPS (EC-MPS) has no impact on GI complications' was a strong unequivocal claim and that Roche had provided no data to support it. The page in question discussed both diarrhoea and GI complications in general and moved seamlessly between the two thus introducing confusion into the mind of the reader about the relative incidence of diarrhoea as a discrete side effect and GI complications as a whole. The Appeal Board noted that the page featured a provocative question followed by a series of selective bullet points. The language used was such that the cumulative effect was to place Myfortic in a disproportionately disadvantaged position such that it was disparaged. The Appeal Board thus upheld the Panel's ruling of a breach of the Code.

Novartis stated that page 9 headed 'Are you concerned about GI complications after transplantation?', implied that it was rarely necessary to alter immunosuppression regimens in patients with GI complications after renal transplantation. Although it was true that dose reduction 'might' be unnecessary, it frequently was. The final bullet point, 'Most GI complications can be treated medically without the need to stop immunosuppression', had no value in the context of transplantation, as stopping immunosuppression was not a practical option because of the almost inevitable consequence of graft rejection and loss. Perhaps the comment was designed to leave the reader with the opinion that GI complications could be treated medically without the need to alter immunosuppression.

Novartis stated that the booklet systematically misled the reader about the relative importance of CellCept in the aetiology of GI complications after transplantation. By misrepresenting the adverse event profile of CellCept, and thereby falsifying its risk benefit profile, Roche was placing patient safety at risk. Roche's consideration of Novartis' comments in 2005, followed by the deliberate reprinting of a larger format item with the continued distortion of the risk benefit profile of CellCept suggested conscious intent.

The Panel considered that the summary page reinforced the impression that the only GI adverse event to be concerned about was diarrhoea. Dose reduction was mentioned but only in the context of being used unnecessarily. The Panel again noted the use of a heading which referred to GI complications as a whole and data which related only to diarrhoea. Overall the Panel considered that the booklet was about the management of diarrhoea post-transplant although many of the headings, claims and the title of the booklet itself, referred to GI complications as a whole. Given the context in which it appeared, ie in a book about the management of diarrhoea, the claim 'Most GI

complications can be treated medically without the need to stop immunnosuppression' implied that diarrhoea in most CellCept patients was due to something other than CellCept. From the data before it the Panel considered that this was misleading. A breach of the Code was ruled.

Although noting its rulings above, the Panel did not consider that the booklet was prejudicial to patient safety and so in that regard it did not warrant a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure and reserved for such use.

Novartis Pharmaceuticals UK Ltd complained about a CellCept (mycophenolate mofetil) booklet (ref P212582/1105) entitled 'Are you concerned about GI [gastrointestinal] complications after transplantation?' issued by Roche Products Limited for use by its hospital sales specialists with transplant specialists and health professionals. CellCept was indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogenic, renal, cardiac or hepatic transplants. Novartis supplied Myfortic (enteric coated mycophenolate sodium) which was also used in combination with ciclosporin and corticosteroids but only for the prophylaxis of acute transplant rejection in adults receiving allogenic renal transplants.

Novartis alleged the booklet breached Clauses 2, 7, 9 and 11 of the Code as it misrepresented the role of immunosuppression, specifically CellCept, in the aetiology of GI complications following transplantation and was inconsistent with the CellCept summary of product characteristics (SPC).

Novartis' principal concern related to how the safety profile of CellCept was presented. The piece was designed in the style of an educational booklet on GI complications after transplant surgery, however its underlying intent was to distance CellCept from its well recognised association with GI complications. The overall impression was that infection, rather than immunosuppression, was the main cause of GI adverse events during CellCept therapy. In contrast, the CellCept SPC listed vomiting, abdominal pain, diarrhoea and nausea as being very common and GI haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence and eructation as being common during therapy. The SPC also stated under 'Special warnings and precautions for use' that 'oversuppression of the immune system increases the susceptibility to infection including opportunistic infections, fatal infections and sepsis'.

Roche rejected the allegation that it was attempting to mislead the transplant community as to the relationship between CellCept and GI adverse events. The booklet was not inconsistent with the SPC and it gave a fair, clinically relevant, and balanced review of the issues at hand. Roche wanted to encourage rational prescribing and to preserve graft viability, in accordance with the following rationale:

1 The safety of the patient and their graft was paramount.

2 Diarrhoea was a significant concern when managing transplant recipients, and might be related to immunosuppression.

3 There were other causes of diarrhoea that should be considered (and treated where appropriate) before reducing or altering immunosuppression.

4 Reducing or altering immunosuppression had been shown to increase the risk of acute rejection episodes, and graft loss at 3 years graft (Knoll *et al*, 2003; Pelletier *et al*, 2003).

The booklet at issue was withdrawn in April 2006.

1 Page 1: 'GI complications in transplantation'

COMPLAINT

A list of causes of GI adverse events was given, with infections at the top and finishing with drug-induced effects, for example antibiotics and immunosuppressants, at the bottom. Novartis believed this oversimplified the aetiology of GI adverse events in order to minimise the association with CellCept. In intercompany correspondence, Roche had previously suggested that the position of immunosuppression at the bottom of the list was 'visually prominent'; however Novartis believed that this was inconsistent with accepted conventions of hierarchy in the presentation of information. In the context of a CellCept branded promotional piece, and in view of the prominence of GI side effects in the CellCept SPC, immunosuppression (if not specifically CellCept) should occupy first position in any ranking of causes for GI side effects after transplantation; both because it was directly toxic to the GI tract and because it was a potent immunosuppressant that increased the risk of infections which might be associated with GI symptoms. Breaches of Clauses 7.2, 7.8, 7.9 and 7.10 were alleged.

RESPONSE

Roche stated that, as there were no figures for incidences presented for any of the potential causes given or numbering of points, it disagreed that this list imparted any special sense of hierarchy. For instance, a list of particulars such as age, sex, date of birth, was similarly without hierarchy.

On the contrary, the positioning of 'immunosuppressants' at the end of the list was visually quite impactful. Furthermore, the paragraph preceding the list stated 'The use of CellCept has led to significant reductions in graft rejection and improved long-term graft survival and function, but GI effects are still a concern with immunosuppression'. Therefore, Roche believed it had appropriately highlighted the association of immunosuppression, and CellCept, with GI adverse events.

PANEL RULING

The Panel noted from the CellCept SPC that treatment should be initiated and maintained by appropriately qualified transplant specialists; it would thus be prescribed by individuals with a great deal of knowledge in the therapy area. The undesirable effects section of the CellCept SPC stated that the

principal adverse reactions associated with the administration of CellCept in combination with ciclosporin and corticosteroids included diarrhoea, leucopenia, sepsis and vomiting and there was evidence of a higher frequency of certain types of infection. Under a sub-heading of 'Opportunistic infections', the SPC also stated that all transplant patients were at increased risk of opportunistic infections; the risk increased with total immunosuppressive load. The most common infections in patients followed for at least one year were candida mucocutaneous, CMV viraemia/syndrome and herpes simplex. With regard to GI adverse reactions, vomiting, abdominal pain, diarrhoea and nausea were listed as very common (≥1/10) and GI haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence and eructation were listed as common (≥ 1/100 to < 1/10).

The Panel noted that the page was headed 'GI complications in transplantation'. No specific mention was made regarding GI adverse events with CellCept. The page stated that 'The use of CellCept has led to significant reductions in graft rejection and improved long-term graft survival and function, but GI effects are still a concern with immunosupression'. Drug-induced effects were included on the list of causes of GI adverse events. The list did not give any indication of the incidence or ranking of the importance of infection, surgery, concomitant diseases or drugs in causing GI complications. The Panel noted that Rubin (2001) stated that it was often very difficult to distinguish between infection-related and immunosuppression-related GI complications after transplantation. The causes might differ depending upon the amount of time post-transplant and this time line was helpful in determining whether a GI complication was likely to be related to infection rather than a specific effect of an immunosuppressant medicine.

The Panel did not accept that the list oversimplified the aetiology of GI adverse events. The booklet was aimed at a specialised audience. Thus the Panel ruled no breach of Clauses 7.2, 7.8, 7.9 and 7.10 of the Code.

2 Page 2: 'GI complications in transplantation'

Page 2 was sub headed 'Determining the probable cause can prove a prudent course of action' and included two quotations:

> 'Inappropriate dose reduction of an immunosuppressive agent that may not be the cause of the diarrhoea may result in an unnecessarily increased risk of acute rejection, the long-term impact of which is far more detrimental to patient or graft survival.' (Pescovitz *et al* 2001) and 'As infections very often have GI symptoms, it is important to rule out infection before looking to the immunosuppressive drug regimen as the cause of a patient's GI problem.' (Rubin 2001).

COMPLAINT

Novartis alleged that the two quotations from a 2001 journal supplement suggested that intervention to reduce GI side effects during Cellcept therapy should be delayed until GI symptoms had been investigated and created the impression that the true cause was frequently independent of the dose of immunosuppression given. As detailed above, these views were not consistent with the CellCept SPC. In addition, it was not made clear that the quotations represented opinions expressed in a journal supplement which had not been peer-reviewed rather than the evidence based conclusion of a study. Breaches of Clauses 7.2, 7.4, 7.6, 7.10, 11.4 were alleged.

RESPONSE

Roche noted that none of the statements in the SPC stated that CellCept alone caused GI complications. The SPC provided no detail as to the actual underlying cause of the GI events for example whether they resulted from a direct effect of CellCept and/or its use in combination immunosuppression, or indirectly due to opportunistic infection arising from over immunosuppression with CellCept in combination with other immunosuppressants. Furthermore, there was no recommendation for dose reduction of CellCept in terms of managing either GI adverse events or infections. Therefore Roche did not believe that the statements were inconsistent with the CellCept SPC.

The quotations came from review articles contained in a supplement to a peer-reviewed journal, Clinical Transplantation. These comments represented current medical thinking, as demonstrated by a quotation from a recent peer-reviewed publication of a prospective study examining the relationship between immunosuppression and diarrhoea:

> 'As changes to immunosuppressive therapy can be the result of perceived drug-related adverse effects, and as such changes are associated with an increased risk of acute rejection, it seems imperative that the cause of GI complications in patients receiving immunosuppressant therapy should be fully investigated.' (Maes *et al*, 2006).

PANEL RULING

The Panel did not consider that the page was inconsistent with the CellCept SPC as alleged. The CellCept SPC listed GI adverse events as well as generally linking immunosuppression to infections. The specialist audience would be well aware of the difficulties with immunosuppression treatment. It was a matter for the specialists to decide whether to lower the dose of CellCept and when this should happen. The Panel did not accept that the page gave the impression that the true cause of GI complications was frequently independent of the dose of immunosupressant used. In the Panel's view the main message of the page was summed up in the sub-heading 'Determining the probable cause can prove to be a prudent course of action'.

The Panel did not consider that the Code required promotional material to indicate that a quotation had been taken from a source that had not been peer-reviewed as alleged. The Code required quotations to

be factual and accurate and not misleading. The source needed to be cited.

The Panel considered that on the evidence before it there was no breach of Clauses 7.2, 7.4, 7.6, 7.10 and 11.4 of the Code.

3 Page 3: 'Managing GI adverse events'

Page 3 was sub headed 'The proven benefit of excluding infection' and presented data from Maes *et al* (2003) on 26 renal transplant patients on an immunosuppressive regime which included CellCept. An infectious cause of diarrhoea was demonstrated in approximately 60% (n=13). A graph was included which showed that of those thirteen patients 92% (n=12) had diarrhoea primarily treated with antimicrobial agents; in the remaining patient, with a concomitant malignant disorder, immunosuppressant therapy was stopped. The page concluded that 'Diarrhoea was successfully treated with antimicrobial agents without the need for permanent reduction or cessation of immunosuppressant'.

COMPLAINT

Novartis alleged that the strong claim of the 'proven' benefit of excluding infection was not supported by the data presented. Half of the 26 patients with diarrhoea, selected as a subset of 765 patients, had an infectious cause of their diarrhoea. This was clearly not a 'proven benefit', particularly when one considered that CellCept itself predisposed to infection through immunosuppression. Furthermore, the use of a graph with an impressive 92% graphic created a misleading impression of robust support for the claim.

The data presented related specifically to persistent afebrile diarrhoea but the headings were 'Managing GI adverse events' and 'The proven benefit of excluding infection'. Diarrhoea was only one of the GI adverse events listed in the CellCept SPC and no evidence was supplied for the benefit of excluding infection in the remainder; vomiting, abdominal pain, nausea, GI haemorrhage, peritonitis, ileus, colitis, gastric ulcer, duodenal ulcer, gastritis, oesophagitis, stomatitis, constipation, dyspepsia, flatulence and eructation. Breaches of Clauses 7.2, 7.4, 7.8, 7.10, 9.1 were alleged.

RESPONSE

Roche stated it was difficult to understand the thinking behind Novartis' concern. Anyone involved in transplantation would know that excluding infection should be a major safety consideration to avoid inappropriate reduction of immunosuppression, increasing the risk of rejection and graft loss. Maes *et al* had proven the benefit of examining non-immunosuppressant causes of diarrhoea, whereby management of symptoms did not always require reduction of immunosuppression. The study showed that a proportion of patients had resolution of their diarrhoea when infectious causes were investigated and treated accordingly. This was achieved without major change to the patient's immunosuppression, and was therefore more beneficial in terms of the patient and the healthcare system.

The title of this page was but one page examining GI adverse events in this item. Clearly, the main GI adverse event of concern was diarrhoea, due to the negative impact of dehydration on graft function.

PANEL RULING

The Panel noted that the page headed 'Managing GI adverse events' featured a graph showing that 92% of patients had diarrhoea treated primarily with antimicrobial agents. The sub-heading to the page read 'The proven benefit of excluding infection'. The Panel considered that at first glance the page seemed to suggest that in 92% of patients with GI adverse events, diarrhoea could be controlled with antimicrobials without the need to reduce the dose of immunosuppressant. This was not the case. The 92% related to the subset of patients with persistent afebrile diarrhoea in whom an infectious cause was found ie 13 patients. In the other patients in whom no infection was determined, immunosuppressive therapy was either reduced or stopped. Thus in an original group of 26 patients with afebrile diarrhoea, an infectious cause was demonstrated in 13, only 12 of whom were successfully treated with antibiotics ie <50% (12/26) as opposed to the 92% (12/13) depicted in the graph. The Panel considered that the page was misleading in this regard. The Panel also considered that it was misleading for a page headed 'Managing GI adverse events' to focus only on data in patients with persistent afebrile diarrhoea. The heading related to all GI adverse events but the data shown related to only one specific effect. Breaches of Clauses 7.2, 7.4 and 7.10 were ruled.

The graph presented the data accurately but in the Panel's view was not presented in such a way as to give a clear, fair, balanced view of the data. It was visually misleading. A breach of Clause 7.8 of the Code was ruled.

The Panel did not consider that the page failed to maintain a high standard and thus no breach of Clause 9.1 of the Code was ruled.

4 Pages 4 and 5: 'Managing GI adverse events' and 'Managing infectious diarrhoea'

COMPLAINT

Novartis stated that these pages contributed to the impression that infection was the most important cause of GI upset and that it was independent of immunosuppression (Cellcept). The treatment algorithm suggested that immunosuppression should only be considered a cause for GI upset once infection had been excluded. It was interesting to note that the first version of this booklet included a similar flow chart and referenced Behrend (2001). Novartis pointed out to Roche that Behrend advocated an entirely different, and more widely accepted, approach of careful review of medication, particularly immunosuppressant, with a view to reducing or splitting the dose of CellCept early in the management of GI adverse events. The current version of the algorithm clearly took these comments into account as Behrend was no longer cited, but the content remained similarly unbalanced. Breaches of Clauses 7.2, 7.4, 9.1 were alleged.

RESPONSE

Roche rejected the assertion by Novartis that these two pages implied that infection was the most important cause of GI adverse effects, and that it was independent of immunosuppression (CellCept). There were no statements on either page that supported this complaint.

Roche intended the two pages to present distinguishing features of infection versus immunosuppression-related GI adverse events, and a proposal for a suggested approach for managing infection-related diarrhoea. This was in line with the main aim of the item, whereby other causes of diarrhoea should be considered before reducing or altering immunosuppression and putting the graft at risk. Should infection as a cause be excluded, page 6 went on to provide suggestions for managing non-infectious/drug-induced diarrhoea, including reduction of immunosuppressive therapy.

Roche had taken previous comments made by Novartis and reviewed the referencing to avoid inconsistencies with the CellCept SPC, which did not recommend dose reduction for GI adverse events.

PANEL RULING

The Panel did not consider that pages 4 and 5 implied that infection was the most important cause of GI upset and that this was independent of the immunosupression. The subheading implied that it was important to distinguish between infection-related and immunosuppression-related GI complications. In the Panel's view the pages encouraged a pragmatic approach ie that the cause of diarrhoea should be established before any treatment changes were introduced. The Panel did not consider that the pages were misleading and thus ruled no breach of Clauses 7.2, 7.4 and 9.1 of the Code.

5 Page 7: 'Managing non-infectious diarrhoea'

The page referred to 10 patients of the 23 patients with afebrile diarrhoea that did not have an infectious cause and were presumed to have drug-induced diarrhoea (Maes *et al*). This was followed by 'All immunosuppressant regimens are associated with diarrhoea to a greater or lesser extent'.

The frequency of study-reported diarrhoea post transplantation was given in a table.

COMPLAINT

Novartis stated that in an attempt to create a perception that the licensed use of CellCept was no more associated with GI adverse events than other immunosuppressants, GI adverse event rates seen with a number of alternative regimens were presented under the heading 'Frequency of study-reported diarrhoea post transplantation'.

The combination of tacrolimus and CellCept was not licensed. The regimen of ciclosporin and sirolimus was licensed; however the continuation of the combination beyond three months (as per the reference cited) was specifically contraindicated in the sirolimus SPC, making this another unlicensed safety claim. A breach of Clause 7.10 was alleged.

RESPONSE

Roche stated that this table was presented under the statement 'All immunosuppressant regimens are associated with diarrhoea to a greater or lesser extent', and reported the incidence of diarrhoea from randomised, controlled trials of different immunosuppressant combinations in de novo transplant recipients (as this was the population most likely to experience GI problems).

For the ciclosporin and sirolimus combination, the frequency of diarrhoea reported in both the sirolimus SPC and the pivotal studies cited were for the combination with ciclosporin and steroids.

Furthermore, the combination of CellCept and tacrolimus was reviewed in the CellCept SPC (section 4.2), which described a pharmacokinetic interaction resulting in increased exposure to mycophenolic acid in both renal and liver transplant recipients, an outcome of which might be increased side effects. As such, Roche did not believe it was inconsistent with the SPC to quote the incidence of diarrhoea for this combination. The presentation of information not cited in the licensed indication but related to other parts of the SPC, had previously been ruled as not inconsistent with SPC, and therefore allowable within the Code (Case AUTH/1100/11/00). No claim was being made about the efficacy of the combination of CellCept and tacrolimus, only useful safety data in accordance with the SPC. In addition, the combination of tacrolimus and CellCept in cardiac transplantation had recently been added to the tacrolimus SPC.

Roche believed that the nature and context in which the information presented in this table complied with the requirements of the Code.

PANEL RULING

The Panel noted that the combination of CellCept and tacrolimus was not mentioned in the therapeutic indications, Section 4.1, of the CellCept SPC. Mention was made in Section 4.5 interactions. The Panel did not consider that in the context of the table it was unreasonable to include details of the frequency of diarrhoea with this combination. Ciclosporin and sirolimus were licensed for use for 3 months. The Panel did not consider that in the context of the page at issue the information about the frequency of diarrhoea with regard to CellCept and tacrolimus and ciclosporin and sirolimus were unlicensed safely claims as alleged. No breach of Clause 7.10 of the Code was ruled.

The Panel considered that the information could have been better presented to make the limitations clear.

6 Page 8: 'Managing non-infectious diarrhoea'

Page 8 of the booklet was headed 'Managing non-infectious diarrhoea' and sub headed 'Is there a role for enteric-coated mycopenolate sodium (EC-MPS) [Myfortic] in reducing GI complications?' followed by:

- 'The safety and tolerability of IV CellCept was assessed in a double-blind comparison with oral CellCept. GI adverse events such as vomiting and diarrhoea previously seen with the oral formulation, were not avoided with the IV formulation of CellCept.
- This supports the hypothesis that diarrhoea is not simply a topical effect of CellCept
- Moreover, gastro-resistant dosage forms claim to protect to mucosa of the stomach only, not that of the intestine

As such, it is not surprising that the enteric coat to MPS (EC-MPS) has no impact on GI complications:

- EC-MPS causes similar levels of GI adverse events to CellCept [Salvadori *et al* 2003]
- In a study comparing the two treatments, the rate of diarrhoea at three months were 4.9% (CellCept) and 5.0% (EC-MPS)
- EC-MPS has no advantage on tolerability over CellCept and no proven role in patients failing to tolerate CellCept.'

COMPLAINT

Novartis alleged that this page disparaged its product, Myfortic. It presented a hypothesis based on a single bioavailability study that compared oral and IV administration of CellCept (ie a study that did not contain the product being denigrated). The hypothesis, which relied on the faulty premise of a single potential mechanism (topical effect), was used to support the statement 'As such, it is not surprising that the enteric coat of MPS has no impact on GI complications'. It ignored alternative potential mechanisms, such as pharmacokinetic differences between the products.

The rather definitive statement 'EC-MPS has no advantage on tolerability over CellCept and no proven role in patients failing to tolerate CellCept', was referenced to a letter of opinion, written by a single clinician and in French, and was not an evidence based conclusion. Data comparing the rate of diarrhoea with CellCept and Myfortic was taken from a study which excluded patients unable to tolerate CellCept and as such provided little insight into the relative tolerability of the two agents. The statement also ignored that fact that the exploration of potential GI differences between the products remained the subject of a study involving more than half of the renal transplant centres in the UK. This careful and unbalanced selection of data disparaged Myfortic in breach of Clause 8.1.

RESPONSE

Roche disagreed with Novartis that the information presented regarding EC-MPS and GI adverse events was disparaging. The statements reflected outcomes from randomized, controlled registration studies, which showed that EC-MPS provided no clinical benefit over CellCept in terms of GI adverse events. Including unproven theory and conjecture (as Novartis had cited), without any supporting clinical benefit of enteric-coating, was irrelevant.

PANEL RULING

The Panel noted that Salvadori *et al* (2003) compared CellCept (1000mg bid) with Myfortic (720mg bid) and concluded that the products were therapeutically equivalent with a comparable safety profile. Within 12 months 15% of Myfortic and 19.5% of CellCept patients required dose changes for GI adverse events (p=ns). The study was not designed to statistically detect differences between treatment groups in terms of GI tolerability. The claim that [Myfortic] had no impact on GI complications was a strong one. The Panel noted that although the claim '[Myfortic] has no advantage on tolerability over CellCept and no proven role in patients failing to tolerate CellCept' was referenced to Marquet (2004), it appeared to be a quotation in that paper from the Transparency Commission decision concerning Myfortic, French Republic 2004. 'However it should be noted that according to current knowledge, Myfortic has no advantage in tolerability over CellCept and has no proven role in patients failing to tolerate CellCept.' This was more than the opinion of a single clinician. Novartis had not submitted data to support its complaint although a study was ongoing.

The comparison of rates of diarrhoea were from Budde *et al* (2003). The discussion noted that patients entered into the study were receiving and therefore tolerating [CellCept] at a dose of 2000mg which might introduce a bias as this population might not be representative of the overall transplant population. The Panel considered that the page had not put this data in context. It was inappropriate to follow the subheading 'Is there a role for enteric coated mycophenolate sodium (EC-MPS) in reducing GI complications' with data referring only to CellCept.

The Panel noted that according to the SPCs for CellCept and Myfortic, diarrhoea was a very common side effect with both (≥ 10%). However the other very common GI side effects of CellCept (vomiting, abdominal pain and nausea) only occurred commonly (≥ 1% and <10%) with Myfortic. Similarly some of the commonly occurring GI disorders with CellCept (eructation, ileus, oesophagitis, gastrointestinal haemorrhage) were uncommon (≥ 0.1% and <1%) with Myfortic. Thus, although both products were associated with a number of similar GI disorders there seemed to be a lessening of effect with Myfortic.

The Panel again noted that subheadings referred to GI complications as a whole whereas some of the data presented referred specifically to diarrhoea.

On balance the Panel considered that the page disparaged Myfortic and a breach of Clause 8.1 of the Code was ruled. This ruling was appealed.

APPEAL BY ROCHE

Roche submitted that the point of this page was not to disparage Myfortic, but to illustrate that no evidence existed to show any additional benefit of Myfortic or any enteric-coated formulations of mycophenolic acid (MPA – the shared active moiety) over CellCept in terms of diarrhoea, the major GI problem for transplant recipients.

Roche explained that the intention of the section sub-

headed 'Is there a role for enteric-coated mycophenolate sodium (EC-MPS) in reducing GI complications?' was to highlight the available clinical evidence that suggested MPA-related diarrhoea was not simply the result of a topical effect, but was largely due to systemic exposure of MPA and/or its metabolites. Thus, an enteric-coated formulation of MPA was not likely to significantly reduce diarrhoea. This hypothesis was supported originally by the finding that rates of diarrhoea and vomiting were not reduced in the comparison of intravenous vs oral mycophenolate mofetil (Pescovitz *et al*, 2001). Whilst the Panel stated that it was inappropriate to follow the sub-heading with data referring only to CellCept, unfortunately there was no equivalent data for Myfortic (ie oral vs systemic administration) available. Furthermore, it was not possible to present the case for Myfortic reducing any GI complications (including diarrhoea), since none existed even though the molecule was developed with the hope of reducing GI adverse events. Therefore, Roche submitted that the sub-heading was fair and balanced on the basis of available data.

Roche noted the sub-heading 'As such, it is not surprising that the enteric coat of MPS (EC-MPS) has no impact on GI complications'. Roche submitted that the claim of 'no impact' or additional benefit of Myfortic was based on the fact that there was no published, randomised, controlled trial (RCT) comparing Myfortic and CellCept that had demonstrated a statistically significant benefit for any GI outcome. This fact was reflected in the findings of the French Republic's Transparency Commission decision concerning Myfortic (referenced on the same page of the booklet) (Marquet), which stated: 'However it should be noted that according to current knowledge, Myfortic has no advantage in tolerability over CellCept and has no proven role in patients failing to tolerate CellCept'.

Roche acknowledged and accepted the Panel's points regarding the use of the two Novartis pivotal studies (Salvadori *et al*, and Budde *et al*, 2003), which could have been presented more clearly. However, as the intention was to present the only robust data available on the comparison of GI adverse events (and specifically diarrhoea) from RCTs, the omission to qualify the limitations of the Novartis data did not constitute disparagement.

The only new data from a randomised, controlled study to become available since the preparation of this booklet was a comparison of Myfortic and CellCept in cardiac transplantation (Kobashigawa *et al*, 2006). Whilst this study had a number of limitations (ie single-blind, no blinding of formulations), and was not powered for safety outcomes, the GI adverse event profiles were provided.

Kobashigawa *et al*, Salvadori *et al* and Budde *et al*, showed no clear trend favouring either CellCept or Myfortic in terms of GI adverse events. With regards to the claims made on page 8 of the booklet, Roche submitted that it had not implied that Myfortic was worse than CellCept but showed that Myfortic offered no GI advantage.

As there was no prospective, randomised clinical trial evidence to support a benefit of Myfortic over CellCept, it appeared that the Panel had based the ruling of disparagement on a comparison of the SPCs for Myfortic and CellCept stating: 'Thus, although both products were associated with a number of similar GI disorders, there seemed to be a lessening of effect with Myfortic'. However, such a comparison was inappropriate as there were substantial differences in the populations represented, and attendant clinical conditions. The table below compared the pivotal studies from which the adverse events were reported for CellCept and Myfortic.

Patient population	*Dose studied (grams/day)*	*No. patients in safety population*
CellCept		
Renal –		
de novo recipients	2	501
Cardiac –		
de novo recipients	3	289
Liver –		
de novo recipients	3	278
Total		1068
Myfortic		
Renal –		
de novo recipients	1.44	213
Renal –		
maintenance recipients	1.44	159
Total		372

As there were differences in the number and populations of transplant recipients (both organ type and timing of introduction of therapy), as well as the doses studied, it was invalid to make direct comparisons of the GI adverse event profiles listed in the CellCept and Myfortic SPCs. Furthermore, in its comparison the Panel made an assumption about the impact of Myfortic on GI disorders without prospective RCT evidence to support it.

In summary, Roche submitted that the claims were fair, balanced and based on the available evidence base. The absence of robust data to support Myfortic's position should not be construed as disparagement.

COMMENTS FROM NOVARTIS

Novartis submitted that the mechanism of MPA-induced GI side effects and the selection of appropriate interventions for individual patients were topics of considerable research and debate. Despite this, Roche sought to justify definitive statements that disparaged the enteric coated nature of Myfortic (EC-MPS) and made absolute statements about the effect of Myfortic on GI complications. For example:

> 'EC-MPS has no impact on GI complications'
> 'EC-MPS has no advantage on tolerability over Cellcept' and
> 'no proven role in patients failing to tolerate Cellcept'.

Novartis alleged that the page in question created the perception that the enteric coat of Myfortic had no

role in reducing GI side effects. This perception was not substantiable and disparaged Myfortic.

After creating the impression of a theoretical basis for a lack of benefit to Myfortic's enteric coat, the page went on to claim that this had been clinically proven by use of the statement, 'As such it is not surprising that the enteric coat of MPS (EC-MPS) has no impact on GI complications'. Again this conclusion was substantiable and disparaged Myfortic.

The comparative GI tolerability of Myfortic and Cellcept remained the subject of debate and research. The majority of renal transplant centres in the UK were recruiting patients into a randomised study to compare the GI tolerability of the two. Had the question been resolved with the certitude proposed by Roche, Novartis would not have embarked on such a study nor would it have obtained independent Ethics Committee approval for its conduct.

Clearly a complex scientific question remained to be definitively answered through further research; pharmaceutical companies should not attempt to resolve it in the minds of prescribers by disparaging competitor products.

Novartis noted the claims 'The safety and tolerability of IV Cellcept was assessed in a double-blind comparison with oral Cellcept. GI adverse events such as vomiting and diarrhoea previously seen with the oral formulation, were not avoided with the IV formulation of Cellcept' (Pescovitz *et al*) and 'This supports the hypothesis that diarrhoea is not simply a topical effect of Cellcept' (Pescovitz *et al*). Novartis submitted that Pescovitz *et al* was not of sufficient quality to make comparative assessments of the tolerability of oral vs IV Cellcept. This study was presented as a double-blind comparison of oral and IV Cellcept yet both arms were given open label oral Cellcept for the majority of the study. The MPA exposures of the IV and oral formulations were not bioequivalent. The only period of direct comparison was the first 5 days after transplantation, when patients were recovering from major abdominal surgery, were frequently nil by mouth and were receiving antibiotics and opioid analgesia. This was clearly not representative of the potentially lifelong, chronic nature of MPA therapy after transplantation.

Pescovitz *et al* pertained to Cellcept but was presented under a subheading relating to EC-MPS. This was considered inappropriate by the Panel. In its appeal, Roche had tried to justify the extrapolation of Cellcept data to Myfortic by referring to the absence of equivalent data for Myfortic. It was hard to see how such data could ever be meaningfully generated when one considered the enteric coated nature of Myfortic.

The question of whether MPA toxicity was topical or systemic had not been resolved in favour of either mechanism. Current consensus favoured a complex, mixed aetiology but neither mechanism would preclude a role for an enteric coat in reducing GI side effects of MPA. Evidence to suggest a systemic cause did not mean that a local irritant effect of high local concentrations in the gut wall could be excluded. Even Pescovitz *et al* was cautious not to oversimplify the hypothesis: 'perhaps agents that do not dissolve in the stomach may have less local toxicity, such as nausea or dyspepsia. The implication of the concentration controlled trial data was that if you can spread the dose of MMF, for example, over the day, you can reduce some of the local toxicity, but that this is more likely to avoid proximal GI symptomatology than distal'.

In Hale *et al* (1998), GI toxicity was more closely correlated with the oral dose of MMF given than with systemic exposure achieved. The authors stated, 'It is possible that the risk of diarrhoea better relates to dose than a pharmacokinetic variable because the mechanistic basis of the event may be a local one acting within the gastrointestinal tract'.

An enteric coat might alter the tolerability profile of a medicine by altering pharmacokinetic variables. It was entirely reasonable that the enteric coat, by modifying parameters such as Cmax in individual patients prone to GI side effects of the Cellcept formulation, might have a role in reducing GI complications.

Mourad *et al* (2001) had demonstrated that, at a fixed dose of 2g/day, a high MPA concentration at 30 minutes was associated with an increased risk of side effects.

A common strategy to limit GI complications with Cellcept was to split the dosing from twice daily to three (or four) times daily or to dose Cellcept with food (Behrend 2001). Both of these interventions effectively reduced the Cmax.

As stated in the SPC and by Roche at the base of the page in question, the pharmacokinetic profile of Myfortic differed from that of Cellcept. This provided a theoretical mechanism for a difference in GI tolerability secondary to an enteric coat.

Novartis considered that the claim 'Moreover, gastro-resistant dosage forms claim to protect the mucosa of the stomach only, not that of the intestine' appeared to assert that avoidance of topical toxicity in the stomach had no role in reducing GI complications. This was misleading because it ignored the existence of upper GI adverse events such as nausea, reflux, vomiting and gastritis.

Novartis noted the claims: 'As such, it is not surprising that the enteric coat of MPS (EC-MPS) has no impact on GI complications', 'EC-MPS causes similar levels of GI adverse events to Cellcept' (Salvadori *et al*) and 'In a study comparing the two treatments, the rates of diarrhoea at three months were 4.9% (Cellcept) and 5% (EC-MPS)' (Budde *et al*).

The two Myfortic Phase III registration studies referred to by Roche did not support the absolute conclusions drawn regarding comparative GI tolerability.

Salvadori *et al* was designed to demonstrate the therapeutic equivalence of EC-MPS and MMF and to compare their safety profiles. In the authors' words, 'It was not designed to statistically detect differences between treatment groups in terms of GI tolerability'.

Budde *et al* required patients to tolerate full dose Cellcept for 4 weeks prior to inclusion in the study, effectively excluding any patients who could not tolerate Cellcept from participation in the trial. This

provided little true insight into the GI tolerability of either product, as evidenced by the extraordinarily low rates of diarrhoea in the study which were quoted by Roche.

Novartis considered that Roche's statement, that it did not believe the omission to qualify the limitations of the Novartis data constituted disparagement, was revealing. Where the limitations of data prevented the generation of accurate or definite conclusions, the data should not be used to support unqualified and absolute statements in promotional material. This principle was not altered by the source of the data.

Novartis noted that Roche referred to Kobashigawa *et al* and presented a table which listed GI adverse event rates. However, Roche had failed to state that patients receiving EC-MPS had fewer dose reductions than MMF patients, which 'might suggest better tolerability of EC-MPS' (authors' quote). The average daily dose (in percent of the nominal dose) was significantly lower in the MMF group (79% vs 88.4%, p = 0.015). Despite higher doses of MPA, patients on EC-MPS had numerically lower rates of diarrhoea (12.8% vs 22.4%, p=0.119). The number of patients in this study was acknowledged to be 'relatively small and might not have been adequate to detect differences in specific side effects'.

Trial design was an important consideration in assessing the GI complications of drug therapy. Particular consideration must be given to the method of collection of GI adverse events.

Pescovitz *et al* discussed the 'inherent difficulties in reporting diarrhoea' such as 'self-reporting and the lack of a standardised questionnaire or even standardised histories obtained by the clinician. For most clinical trials, the report of diarrhoea merely amounted to a tick mark on the patient's case reporting form and little else. There was no basis for qualitative, let alone quantitative comparisons among the diarrhoeal episodes'. The study concluded 'The incidence of diarrhoea and other GI side effects reported for most clinical trials to date is at best unreliable and at worst misleading'.

Studies utilising sensitive, validated patient report instruments were capable of accurately assessing differences in GI tolerability. Studies utilising such instruments in patients suffering GI side effects of Cellcept had shown significant improvement in GI symptoms following conversion to Myfortic and should be acknowledged in any balanced discussion of this subject. Chan *et al* (2006) demonstrated that patients failing to tolerate Cellcept experienced a statistically significant and clinically meaningful reduction in GI symptom burden and an improvement in quality of life following conversion to Myfortic. These conclusions had also been made in a separate, larger, 3 month study (Tomlanovich *et al*).

Novartis noted the claim 'EC-MPS has no advantage on tolerability over Cellcept and no proven role in patients failing to tolerate Cellcept' was taken from Marquet, however the claim included in that review paper, the Panel's ruling and in Roche's appeal was, *'However it should be noted that according to current knowledge,* Myfortic has no advantage in tolerability over Cellcept and no proven role in patients failing to tolerate Cellcept'. The meaning of the quotation was altered by the omission of the qualification in italics; a comment that acknowledged the evolving nature of the evidence base had been altered to create a more definitive one. The review was published in June 2004, before publication of trials using appropriate methodology to compare GI tolerability of Cellcept and Myfortic, and might no longer represent the authors' views.

The incomplete quotation also enabled the misinterpretation, 'There is proof that Myfortic has no role in patients failing to tolerate Cellcept' rather than, 'There is not yet any proof that Myfortic has a role in patients failing to tolerate Cellcept'.

The role of Myfortic in patients *failing to tolerate Cellcept* could not be assessed using the Phase III registrations studies quoted by Roche, as these studies did not enrol patients failing to tolerate Cellcept.

APPEAL BOARD RULING

The Appeal Board noted the clinical data and the parties' submissions thereon together with the products' differing SPCs and pharmacokinetic profiles.

The Appeal Board noted that according to the SPCs for CellCept and Myfortic, diarrhoea was a very common side effect with both (≥ 10%).

The Appeal Board was concerned about the content and layout of the page at issue. It was inappropriate to follow the subheading 'Is there a role for enteric coated mycophenolate sodium (EC-MPS) in reducing GI complications' with data referring only to CellCept. The Appeal Board considered that the claim '… it is not surprising that the enteric coat of MPS (EC-MPS) has no impact on GI complications' was a strong unequivocal claim and that Roche had provided no data to support it. The page in question discussed both diarrhoea and GI complications in general and moved seamlessly between the two thus introducing confusion into the mind of the reader about the relative incidence of diarrhoea as a discrete side effect and GI complications as a whole. The Appeal Board noted that the page at issue featured a provocative question followed by a series of selective bullet points. The language used was such that the cumulative effect was to place Myfortic in a disproportionately disadvantaged position such that it was disparaged. The Appeal Board thus upheld the Panel's ruling of a breach of Clause 8.1 of the Code. The appeal was unsuccessful.

7 Page 9: 'Are you concerned about GI complications after transplantation?'

COMPLAINT

Novartis stated that this summary page implied that it was rarely necessary to alter immunosuppression regimens in patients with GI complications after renal transplantation. Although it was true that dose reduction 'might' be unnecessary, it frequently was. The final bullet point stated that 'Most GI complications can be treated medically without the need to stop immunosuppression'. This comment had

no value in the context of transplantation, as stopping immunosuppression was not a practical option because of the almost inevitable consequence of graft rejection and loss. Perhaps the comment was designed to leave the reader with the opinion that GI complications could be treated medically without the need to alter immunosuppression.

Novartis stated that the booklet systematically misled the reader about the relative importance of CellCept in the aetiology of GI complications after transplantation. By misrepresenting the adverse event profile of CellCept, and thereby falsifying its risk benefit profile, Roche was placing patient safety at risk. Roche's consideration of Novartis' comments in 2005, followed by the deliberate reprinting of a larger format item with the continued distortion of the risk benefit profile of CellCept suggested conscious intent.

RESPONSE

Roche stated that the points made in the summary simply reflected the substance of the booklet, and nowhere did it state or imply that it was rarely necessary to alter immunosuppression.

Roche did not understand Novartis' mixed thinking. On one hand Novartis agreed that whilst reducing the dose of immunosuppression might be unnecessary, it frequently was. Yet unnecessary dose reduction was the very tenet of this item. Also, stopping immunosuppression completely would be in most cases unwarranted. This did not preclude dose reviews.

With regard to the earlier version of the booklet produced in 2005, Novartis raised a number of issues. Roche withdrew the item in order to review the agreed areas of debate, and gave the following undertaking in a letter dated 9 September, 2005:

'Thank you for bringing these matters to our attention. We recognise that there were a number of elements that require further scrutiny and will withdraw this item with immediate effect.'

Roche did not undertake not to release an updated version of the item, and it believed it had met all of the individual undertakings set out in its response.

In conclusion, the booklet at issue was highly regarded and useful, judging from customer feedback, and did not imply that immunosuppression (or indeed CellCept) was not a cause of GI adverse events. To reiterate, this item raised appropriate questions in the expert reader's mind to consider other legitimate causes of GI adverse events (especially diarrhoea) before altering immunosuppressive therapy, which might compromise graft viability and put the patient at further risk.

PANEL RULING

The Panel examined the summary page. In some regards it was simplistic as the consequences of stopping immunosuppression could be serious and would be well known to the audience. It reinforced the impression that the only GI adverse event to be concerned about was diarrhoea. Dose reduction was mentioned but only in the context of being used unnecessarily. The Panel again noted the use of a heading which referred to GI complications as a whole and data which related only to diarrhoea. Overall the Panel considered that the booklet was about the management of diarrhoea post-transplant although many of the headings, claims and the title of the booklet itself, referred to GI complications as a whole. Given the context in which it appeared, ie in a book about the management of diarrhoea, the claim 'Most GI complications can be treated medically without the need to stop immunnosuppression' implied that diarrhoea in most CellCept patients was due to something other than CellCept. From the data before it the Panel considered that this was misleading. A breach of Clause 7.2 was ruled.

Although noting its rulings above, the Panel did not consider that the booklet was prejudicial to patient safety and so in that regard it did not warrant a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure and reserved for such use.

Complaint received **27 June 2006**

Case completed **3 November 2006**

ANONYMOUS EMPLOYEES v MERCK SHARP & DOHME

Medical and educational goods and services

An anonymous complainant raised concerns on behalf of a number of Merck Sharp & Dohme's employees about services offered by the company.

For approximately two years (2002 to 2004) a sales division was responsible for implementing and managing a service which involved placement of bone scanners (DEXA scanners) in general practices to improve the diagnosis of patients with osteoporosis. Sales metrics were considered when deciding which practices should be offered the scanners. Representatives were required to input into the company's electronic territory management system the number of patients that went on to Fosamax (alendronate) as a result of their scan. The conduct of this programme appeared to be in breach of the 2003 Code in the same fashion as the programme at issue in a previous case involving Merck Sharp & Dohme, Case AUTH/1814/3/06.

The Panel noted that a funding proposal included a section on the prescribing environment. The group being considered for receiving a DEXA scanner was said to be currently in the process of updating prescribing guidelines which would include alendronate. Details of the alendronate market share were provided in the proposal.

The Panel noted that a slide set 'DEXA Placements DIY Guide', provided by Merck Sharp & Dohme, was not approved by the company. According to Merck Sharp & Dohme it had been used with a small group of representatives.

One of the slides was headed 'Identify Surgery' listing the criteria as 'sales data, Fosamax target, speaker meeting, influential contact'. For some reason representatives were advised on the day that scanning took place to 'beware of staff'. Inclusion details listed, *inter alia*, 'Rx update FOW/DPMO' and 'sales background'. The sales review criteria were listed as 'market potential, market share FOW vs DPMO, market trend, size market and sales per GP'. Support information included 'GP RX intent'. No official Merck Sharp & Dohme training slides had been submitted.

The checklist for the service, which had also not been authorized by the company, included a list of triggers such as 'GPs are reluctant to start therapy for patients they believe have osteoporosis without a [bone] scan' and 'Fosamax is bisphosphonate of choice'. The outcomes/monitoring included what treatment was initiated if any.

The Panel considered that on the information before it there was no evidence that the representatives had been briefed about the need to separate the provision of medical and educational goods and services from the promotion of medicines. The service would be seen by representatives as being linked to the promotion of Fosamax. This would be reinforced to those representatives shown the slides and given the check list. This was totally unacceptable.

The supplementary information to the 2003 Code stated that materials relating to the provision of medical and educational goods and services must be examined by the Code of Practice signatories and this had not happened with regard to some of the materials. The template letters for patients did not state that the service was sponsored by Merck Sharp & Dohme. The slides linked the provision of the service to the use of Fosamax. The Panel considered that the arrangements were unacceptable. High standards had not been maintained and the circumstances brought discredit upon the pharmaceutical industry; breaches of the Code including Clause 2 were ruled.

The Panel decided to report Merck Sharp & Dohme to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

Upon appeal the Appeal Board noted Merck Sharp & Dohme's submission that the purpose of the programme was to expand the diagnosed population of osteoporotic patients. The programme had started to wind down in the latter half of 2003 from whence no new representatives were trained; only those already trained and experienced on the programme continued to work on it. Managers had continued to provide some training by mentoring in the field. This was one of the reasons for the lack of documentation. Nonetheless, the Appeal Board considered that the company should have been able to produce job bags for the relevant training material which governed the representatives' activities from the latter part of 2003 onwards.

The Appeal Board noted that the company was able to provide little evidence about the provenance, status and use of the slide set 'Placements DIY Guide' and the checklists. The Appeal Board was alarmed at the slide set and concerned that anyone could have produced it. The company's investigation indicated that the slides had been discussed at a best practice meeting typically attended by one representative from each of the six sales regions and four regional managers. The basis of the discussion and its outcome were not known. The Appeal Board considered that there was no evidence on the balance of probabilities that the material had been used to train representatives or had otherwise been disseminated beyond the meeting; or to indicate that it had otherwise influenced the behaviour of representatives in the field.

The Appeal Board further noted another document 'Guide to Proposal Development' which related to funding for osteoporosis selective case finding in primary care. Under a heading of 'Benefits of the project' was stated 'Environment positive for Fosamax with high market share in locality and inclusion in clinical guidelines'. The Appeal Board was concerned at this statement but noted that to the best of Merck Sharp & Dohme's knowledge, no

proposals had ever taken place, nor was there any evidence that the document had influenced representatives' behaviour.

The Appeal Board understood why the Panel was concerned about the material. However, it considered that the complainant had not established on the balance of probabilities that the arrangements amounted to a breach of the Code.

With regard to the Panel's report in accordance with Paragraph 8.2 of the Constitution and Procedure the Appeal Board noted its comments above and its rulings of no breach of the Code. The Appeal Board decided to take no further action.

The complainant alleged that the Special Products Business Unit appeared to engage in 'return on investment' (ROI) calculations in respect of any grants provided to specialist hospital units intended to improve patient care in the relevant therapeutic areas. Such calculations appeared to be at odds with the provision of unconditional grants.

The Panel noted that the complainant acknowledged that he did not have evidence of malpractice. Merck Sharp & Dohme could only identify two unconditional grants as it rarely gave such grants. The business unit manager did not make ROI calculations in relation to grants unrestricted or otherwise. Merck Sharp & Dohme provided evidence relating to two grants to hospitals; one, an educational grant of £10,000 and the other for £1,000 for developments in a cardiac care unit. There was no evidence that ROI calculations had been made. The Panel considered that there was no evidence that Merck Sharp & Dohme had included ROI calculations in relation to grants. Thus no breaches of the Code were ruled.

The complainant alleged that discussion with former members of the Maxalt team would bring into question the probity of conduct in respect of so-called 'switch/upgrade' programmes that were intended to support a change in prescribing at a practice level from GlaxoSmithKline's medicine, Imigran, to Maxalt. Given Maxalt's cost advantages it was not clear whether this practice was at odds with the Code.

The Panel noted that the material supplied by Merck Sharp & Dohme set out the arrangements for a number of migraine therapy review services offered in 2001, 2003 and 2004 onwards. If a practice decided to proceed with such a review a pre-agreed service specification would be signed which was flexible to suit the needs and prescribing habits of the practice. The practice could specify which patients should be included/excluded and set its own preferred treatment algorithm. The doctor was responsible for deciding whether to implement any change in therapy.

It appeared that all of the materials had been seen by the company. The materials did not feature the Maxalt product logo and rarely even used the product name. The Panel noted that a bar chart depicting the percentage of patients with 2 hour headache response featured the Maxalt product name but the Panel did not consider that such use was sufficient to render the material in breach of the Code. There was no representatives' briefing material *per se* provided. On the basis of the material before it there was no evidence that the migraine therapy review was intended to support a switch from Imigran to Maxalt as alleged. No breaches of the Code were ruled.

An anonymous complainant complained on behalf of an undisclosed number of Merck Sharp & Dohme's employees about services offered by Merck Sharp & Dohme Limited.

COMPLAINT

The complainant alleged that in light of recent internal communications regarding the Code breaches relating to Merck Sharp & Dohme's hypertension and diabetes audit programmes supported by the Cozaar product team (Case AUTH/1814/3/06), an unofficial self-appointed group of committed Merck Sharp & Dohme employees, from all sectors of the UK business and with substantial collective experience in sales, had populated the following 'Consensus Statement' of concerns regarding Code adherence by Merck Sharp & Dohme in the UK.

Consensus Statement

Whilst the complainant firmly believed that Merck Sharp & Dohme had contributed significantly to improving the health of the nation through the introduction of numerous innovative medicines during the last three decades and support of several excellent examples of ethical patient care programmes in collaboration with the NHS, the following merited cause for concern in light of the recent Clause 2 breach (Case AUTH/1814/3/06) relating to the hypertension/diabetes nurse advisor programmes:

1 Musculoskeletal Business Unit, FROSST Division: For approximately two years between 2002 and 2004 the FROSST GP Sales Division led by the national sales manager was responsible for implementing a programme which involved one day placement of forearm bone scanners (DEXA scanners) in general practices keen to improve the diagnosis of patients with osteoporosis. Representatives employed within the FROSST division at the time had informed the group that they were required to manage this programme from start to end. Furthermore, sales metrics were considered when decisions were made regarding which practices should be offered the scanners. The group's primary concern related to its finding that representatives were required to input into the company's electronic territory management system (ETMS) the number of patients that went on to Merck's medicine Fosamax (alendronate) as a result of their scan. Accordingly, the conduct of this programme appeared to be in breach of Clause 18.1 of the 2003 Code in exactly the same fashion as the hypertension/diabetes programme in Case AUTH/1814/3/06.

A particular concern in relation to the programme was that the newly appointed Managing Director for Merck Sharp & Dohme in the UK was the FROSST national sales manager's line manager at the time and therefore was presumably completely aware and

agreeable to the manner in which this programme was implemented.

2 Special Products Business Unit: Although the group had not acquired specific evidence of malpractice, the Special Products Business Unit appeared to engage in 'return on investment' (ROI) calculations in respect of any grants provided to specialist hospital units intended to improve patient care in the relevant therapeutic areas. Such ROI calculations appeared to be at odds with the provision of unconditional grants.

3 Migraine Team: Merck Sharp & Dohme had employed a small team devoted to the promotion of its migraine medicine Maxalt for a number of years. Discussion with former members of this team would bring into question the probity of conduct in respect of so-called 'switch/upgrade' programmes that were intended to support a change in prescribing at a practice level from GlaxoSmithKline's medicine, Imigran, to Maxalt. Given the cost advantages provided by Maxalt, the group was not absolutely clear whether this practice was at odds with the Code.

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

RESPONSE

Merck Sharp & Dohme noted that the allegations were unsupported by documents, and were unlimited in time and were, in certain respects, a little difficult to characterise as breaches of the Code. Merck Sharp & Dohme had, however, endeavoured to read the allegations as potential breaches of Clauses 2, 9.1 and 18.1 of the 1998, 2001 and 2003 Codes, since the activities to which the allegations related all took place before January 2006.

Musculoskeletal Business Unit, FROSST Division

Merck Sharp & Dohme submitted that between 2000 and 2004, it had supported a programme whereby general practitioners were offered the services of a radiographer to perform bone density scans on patients identified as being at risk from osteoporosis. The services were provided by a third party and involved the radiographer attending the surgery for one day, during which bone density scans were performed on typically around 25 patients and the results provided to their GP. The patients were identified by the practices themselves and invited to the scanning session by a letter from their own GP. In some cases, the DEXA scanners were purchased by Merck Sharp & Dohme and lent to the third party specialist provider. As a result of the scan, some patients would have been prescribed treatment for osteoporosis.

Merck Sharp & Dohme submitted that its interest in the therapeutic sector prompted its provision of a service. This was the case for most companies. Importantly, however, the prescription of Fosamax Once Weekly was not a condition of the provision of the service and, as far as Merck Sharp & Dohme was aware, at no time was such a representation made to any GP. Fosamax Once Weekly was one of the brand leaders in osteoporosis treatment between 2002 and 2004 and it was likely, therefore, to have been prescribed for a proportion of patients scanned in the DEXA programme. Such prescription would only have taken place after assessment of the patient's suitability for treatment by their GP and a decision by the GP to prescribe Fosamax Once Weekly rather than other available treatments for osteoporosis.

Merck Sharp & Dohme regarded the service as one which both enhanced patient care and benefited the NHS since the availability of bone density scanning to NHS patients was limited, such that a substantial proportion of at risk patients did not have access to bone density scanning at all. The objectives were described in a Merck Sharp & Dohme briefing document drafted in 2001 as to 'Facilitate the earlier diagnosis and active management of osteoporosis in the Primary Care environment' and 'Facilitate the process of implementation of the Royal College of Physicians Bone and Tooth Society guidelines placing greater responsibility with the General Practitioner for the diagnosis and management of the disease'. The service was of particular benefit to patients in rural areas who were able to attend their own surgery for a diagnostic test that might otherwise be available only at a district hospital. It was likely that the majority of at risk patients who were offered scanning were over 60 and would have had risk factors such as previous low trauma facture.

Merck Sharp & Dohme submitted that its representatives told GPs about the DEXA scanning service. Typically, this arose in response to observations made by the GP about the lack of provision of such scanning by their local NHS provider. Although a bone density scan was not a prerequisite to treatment for osteoporosis in at risk patients, it was regarded as best practice and Merck Sharp & Dohme would not encourage physicians to prescribe any osteoporosis treatment without the results of such a scan.

Merck Sharp & Dohme submitted that if the GP wished to take up the offer of the service, the representative would notify his or her manager and contact the third party specialist provider. Thereafter, the third party specialist provider contacted the practice and arranged for the scanning day to take place. The representatives were not involved in the selection of patients. In some cases GPs used template letters provided by the representatives to invite patients to the scanning day and to inform them of their results. In some cases, Merck Sharp & Dohme provided a grant to the practice to help pay for overtime worked by practice nurses in identifying at risk patients.

Merck Sharp & Dohme submitted that it was likely that the representative contacted the practice on the day that the scans were to take place or shortly thereafter to check that the administrative arrangements had gone smoothly. Representatives did not know how many patients were prescribed Fosamax Once Weekly as a result of the scan nor did they have access to any individual patient data. They would, however, be able to infer the approximate number of prescriptions simply from their knowledge of the number of scanning days which had taken

place, the average number of patients scanned who were likely to be diagnosed with osteoporosis and the geographical market share of Fosamax Once Weekly. It was this information which was reported back to their mangers and might, in some cases, have been entered onto the ETMS. However, Merck Sharp & Dohme had examined the information currently held in the ETMS and there seemed to be no available field in which Fosamax Once Weekly sales data linked to the DEXA programme could have been entered. None of the employees interviewed recalled that such data were entered onto the ETMS. The programme finished in 2004.

Merck Sharp & Dohme submitted that it had interviewed the two representatives involved in the programme from 2000 who remained in Merck Sharp & Dohme's employment and had found no evidence to support the allegations. Specifically, while representatives managed some of the administrative arrangements for the programme, the medical and technical aspects were left entirely to the radiographer, the GP and the practice staff. Merck Sharp & Dohme did not consider this to be a breach of Clause 18.1 of the 1998, 2001 or 2003 Codes. The provision of the service was done in such a way as not to be an inducement to prescribe any medicine.

Merck Sharp & Dohme submitted that it had not found any evidence that sales metrics were considered when decisions were made regarding which practices were offered the scanners. None of those interviewed recalled any case of a practice requesting the service being turned down. Indeed, a Merck Sharp & Dohme briefing document describing the funding of osteoporosis projects prepared in 2002 noted that 'No sales data, Return on Investment (ROI) or script impact calculations should be included with the proposal' (provided). Consistent with this, Merck Sharp & Dohme included an example of a completed proposal form in which five benefits of the project were described. The benefits to Merck Sharp & Dohme were described as 'environment positive for Fosamax with high market share in locality and inclusion in clinical guidelines' and 'opportunity for Merck Sharp & Dohme representatives to promote the service to practices thereby offering an added value service'. Clearly, it was likely that practices who requested the service were ones who would consider prescribing Fosamax, since they would have heard about the scanner during a visit from the Fosamax representative. Merck Sharp & Dohme confirmed that it was not its policy only to offer the scanning service to high prescribing practices, although it might be anticipated that it would be expected that such practices would take up the offer in larger numbers than low or non-Fosamax prescribing practices.

Merck Sharp & Dohme provided materials relating to the DEXA programme, given to representatives, nurses, doctors and patients, found in its archives. Merck Sharp & Dohme had not identified formal training materials on the DEXA programme but included in the documents were a number of slide sets of presentations made by managers to representatives. In a few of these documents there was a suggestion that the DEXA programme would lead to increased sales of Fosamax Once Weekly.

Whilst it must be regarded as an inevitability that sales of the market leading product would increase if the use of a diagnostic test which was a prerequisite to its prescription were to increase, there was no suggestion in this documentation that prescribing of Fosamax was a requirement or consideration in the placement of DEXA machines. That said, Merck Sharp & Dohme recognised that it did not represent best practice to reinforce such a suggestion in the minds of representatives. Merck Sharp & Dohme's revised Standard Operating Procedures (SOPs) and training schedule would take account of this.

Merck Sharp & Dohme submitted that during interviews it had been concerned to uncover a set of slides (the 'DEXA Placements DIY Guide' provided) prepared by a representative to present to a small number (less than 10) of selected representatives, managers and marketing specialists at a regional meeting, which it believed mischaracterised the DEXA programme and contained suggestions about its operation that Merck Sharp & Dohme believed did not represent the stated policy objectives of the company or what happened in practice. This slide set was prepared contrary to company policy that representatives should not create their own materials and was not submitted for medico-legal vetting. Revised SOPs and a training schedule would ensure as far as possible that this did not happen again. This slide set appeared to have been produced at the same time and possibly by the same person who drafted a 'DXA checklist'.

In summary Merck Sharp & Dohme did not believe the DEXA programme operated between 2000 and 2004 breached the relevant Codes. There was no evidence of any intention to influence the prescribing habits of GPs or to induce them to prescribe a medicine that they would not otherwise have prescribed. However, the provision of this service enhanced patient care and benefited the NHS. There would be patients in whom fractures and other serious effects of osteoporosis had been prevented because they were able to have a DEXA scan which the NHS was otherwise unable to provide.

Special Products Business Unit

Merck Sharp & Dohme submitted that the allegation in this part of the complaint was difficult to make out. The complainant stated that 'the group had not acquired specific evidence of malpractice'. The most coherent interpretation Merck Sharp & Dohme could put on the complaint was that the Special Products Business Unit had made ROI calculations in respect of the provision of unregistered grants.

Merck Sharp & Dohme noted that the complaint was not limited to a particular time period but it had searched the records of the Special Products Business Unit for the last 18 months and had identified only two grants which could be described as 'unconditional', to use the complainant's term. This was not surprising since the provision of unrestricted grants by Merck Sharp & Dohme was exceedingly rare. It was much more common that grants were provided for specific educational or patient care purposes.

Merck Sharp & Dohme provided all documents

relating to these grants and submitted that there was no suggestion that ROI calculations had been made in relation to either of them. Merck Sharp & Dohme had interviewed the employee who led the Special Products Business Unit, and she confirmed that she did not make such calculations in relation to any grants, unrestricted or otherwise.

Migraine Team

Merck Sharp & Dohme submitted that it was unable to discern a specific allegation in relation to this matter. Merck Sharp & Dohme enclosed a set of archived materials relating to the migraine therapy review audits that it offered to GPs between 2000 and 2005 which it submitted were given to representatives, GPs or patients. There were only two external service providers during that time from January 2004 onwards. The documents used by one were amended and re-approved at the end of 2002. The programme was not intended to, and did not in practice, act as an inducement to doctors to prescribe any specific medicine.

Merck Sharp & Dohme submitted that the selection criteria for practices was their willingness to take part in the programme. Representatives from the team responsible for implementing the programme would make GPs aware of the service as a routine part of all promotional calls during which the customer expressed an interest in the treatment of migraine. If there was a positive response the representative would make a separate appointment and return to discuss the service with the materials. The team involved with implementing the programme was small (15 representatives) and their territories were designed to cover only parts of the country where higher than average amounts of any migraine treatment (not specifically Maxalt) were prescribed. There were no proformas used by the representatives responsible for implementing the programme.

PANEL RULING

The Panel noted that the osteoporosis audit took place prior to 2004/05. Thus the 2003 Code applied; the supplementary information to Clause 18.1 of that Code stated that medical and educational goods and services had to enhance patient care or benefit the NHS. The change under Clause 18.4 of the 2006 Code was that such services had to either enhance patient care or benefit the NHS and maintain patient care and they could not be an inducement to sell any medicine. In addition the provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine.

With regard to therapy review services the supplementary information to Clause 18.4 of the 2006 Code provided helpful guidance. A therapeutic review which aimed to ensure that patients received optimal treatment following a clinical assessment was a legitimate activity for a pharmaceutical company to support and/or assist. The result of such clinical assessments might require, among other things, possible changes of treatment including changes of dose or medicine or cessation of treatment. A genuine therapeutic review should include a comprehensive range of relevant treatment choices, including non-medicinal choices, for the health professional and should not be limited to the medicines of the sponsoring pharmaceutical company. The arrangements for therapeutic review must enhance patient care, or benefit the NHS and maintain patient care. The decision to change or commence treatment must be made for each individual patient by the prescriber and every decision to change an individual patient's treatment must be documented with evidence that it was made on rational grounds.

The supplementary information to Clause 18.1 of the 2003 Code, Provision of Medical and Educational Goods and Services, stated that if representatives provided, delivered or demonstrated medical or educational goods and service then this must not be linked in any way to the promotion of products.

1 DEXA placement in primary care

The Panel considered that the provision of a mobile bone densitometry service would enhance patient care and benefit the NHS. The service had to be provided in such a way as not to be an inducement to prescribe, supply, administer, recommend or buy any medicine (2003 Code).

Fosamax Once Weekly was indicated for the treatment of post-menopausal osteoporosis. Fosamax reduced the risk of vertebral and hip fractures.

The Panel noted that the document 'DEXA placement in Primary Care' stated with regard to appropriate use of DEXA placement that epidemiology suggested that 30% of post-menopausal women were osteoporotic by WHO standards and accordingly of 25 post-menopausal women scanned, statistically 8 would have osteoporotic BMD (bone mineral density). Identification of the highest risk patients would ensure effective utilisation of the technology. The priorities for achieving commercial and personal goals referred to 'Maintain DEXA (market expansion) activities' as a key area for representatives. The project strategy in the briefing document 'Forearm Bone Densitometry' stated that through well researched and rational placement of forearm DEXA technology in the community, co-ordinated through Primary and Secondary Care sectors, Merck Sharp & Dohme would significantly increase the number of patients diagnosed as osteoporotic.

The placement criteria (dated February 2001) stated that to be consistent with the AGO Report, Merck Sharp & Dohme must be seen to be rational in placement of the machines whilst being sensitive to local issues and ensuring that they were used maximally.

The Funding of Osteoporosis Projects briefing document (dated 2002) referred to the project committee consisting of the marketing manager, two national sales managers and two healthcare managers. The document stated that a proposal should include *inter alia* the benefits of the project locally and for Merck Sharp & Dohme. No sales data, ROI, or script impact calculations should be included with the proposal.

A proposal for funding a project was provided and included a section on the prescribing environment. The group being considered for receiving a DEXA machine was said to be currently in the process of updating prescribing guidelines which would include 'Alendronate OW' and would be issued in November 2001. Details of the alendronate market share were provided in the proposal. The date of this proposal was not given. Reference was made to a strategy group meeting on 3 April 2001.

The Panel noted that training slides 'DEXA Placements DIY Guide', provided by Merck Sharp & Dohme, were not approved by the company. According to Merck Sharp & Dohme they had been used with a small group of representatives. No official Merck Sharp & Dohme training slides had been submitted.

The slides provided included one headed 'Identify Surgery' listing the criteria as 'sales data, Fosamax target, speaker meeting, influential contact'. For some reasons representatives were advised on the day that scanning took place to 'beware of staff'. Inclusion details listed, *inter alia*, 'Rx update FOW/DPMO' and 'sales background'. The sales review criteria were listed as 'market potential, market share FOW vs DPMO, market trend, size market and sales per GP'. Support information included 'GP RX intent'.

The DXA checklist, which had also not been authorized by the company, included a list of triggers one of which was that 'GPs are reluctant to start therapy for patients, they believe have osteoporosis without a DXA scan'. Another listed trigger was 'Fosamax is bisphosphonate of choice' , this was emphasised as it was, the only trigger in italics. The outcomes/monitoring included what treatment initiated if any.

The Panel considered that on the information before it there was no evidence that the representatives had been briefed about the need to separate the provision of medical and educational goods and services from the promotion of medicines. The service would be seen by representatives as being linked to the promotion of Fosamax. This would be reinforced to those representatives shown the training slides and given the DXA check list. This was totally unacceptable.

Under the supplementary information to Clause 18.1 of the 2003 Code materials relating to the provision of medical and educational goods and services must be examined by the Code of Practice signatories. This had not happened with regard to some of the materials.

The template letters for patients did not state that the service was sponsored by Merck Sharp & Dohme.

The Panel considered that the programme did not meet the requirements of Clause 18.1 of the Code. The training slides linked the provision of the service to the use of Fosamax. The Panel considered that the arrangements were unacceptable in relation to Clause 18.1 and ruled accordingly. This ruling was appealed.

The Panel considered that high standards had not been maintained and the circumstances brought discredit upon the pharmaceutical industry; breaches of Clauses 9.1 and 2 were ruled. These rulings were appealed.

The Panel decided to report Merck Sharp & Dohme to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure.

2 Special Products Business Unit

The Panel noted that the complainant acknowledged that he did not have specific evidence of malpractice and it appeared that ROI calculations were made regarding grants to specialist hospital units. Merck Sharp & Dohme could only identify two unconditional grants which it submitted was not unexpected as the company rarely gave unconditional grants. More commonly the company gave grants for specific purposes. The business unit manager did not make such calculations in relation to grants unrestricted or otherwise.

The paperwork provided by Merck Sharp & Dohme related to two grants to hospitals. One was an educational grant of £10,000 and the other was for £1,000 for developments in a cardiac care unit. There was no evidence that ROI calculations had been made.

The Panel considered that there was no evidence that Merck Sharp & Dohme had included ROI calculations in relation to grants. Thus no breach of Clauses 18.1, 9.1 and 2 was ruled.

3 Migraine Team

The Panel noted that the complainant was not clear whether the switch/upgrade programmes intended to support a change from Imigran to Maxalt were at odds with the Code. The complainant had not given any details of his/her specific concerns in this regard.

The material supplied by Merck Sharp & Dohme set out the arrangements for a number of migraine therapy review services offered in 2001, 2003 and 2004 onwards. If a practice decided to proceed with such a review a pre-agreed service specification would be signed which was flexible to suit the needs and prescribing habits of the practice. The practice could specify which patients should be included/excluded and set its own preferred treatment algorithm. The doctor was responsible for deciding whether to implement any change in therapy.

It appeared that all of the materials had been seen by the company. The materials did not feature the Maxalt product logo and rarely even used the product name. The Panel noted that a bar chart depicting the percentage of patients with 2 hour headache response did feature the Maxalt product name but the Panel did not consider that such use was sufficient to render the material in breach of the Code. There was no representatives' briefing material *per se* provided. On the basis of the material before it there was no evidence that the migraine therapy review was intended to support a switch from Imigran to Maxalt as alleged. No breach of Clauses 18.1, 9.1 and 2 was ruled.

APPEAL BY MERCK SHARP & DOHME

Merck Sharp & Dohme appealed the Panel's rulings of breaches of Clauses 2, 9.1 and 18.1 of the 2003 Code with regard to its funding of a community based service in support of the diagnosis of osteoporosis between 2000 and 2004.

Merck Sharp & Dohme submitted that the factual findings of the Panel on which the rulings of breaches of the Code were made were not the basis for the original complaint. The Panel's ruling on the allegation of a breach of Clause 18.1 of the 2003 Code stated that: the Panel did not have before it evidence that representatives had been briefed about the need to separate the provision of medical and educational goods and services from the promotion of medicines; and the materials relating to the DEXA service had not been reviewed; and the training slides linked the provision of the DEXA service to use of Fosamax; and the template letters for patients did not state that the service was sponsored by Merck Sharp & Dohme.

Merck Sharp & Dohme acknowledged that it was unable to provide the Panel with formal representatives' training material that it could demonstrate had been examined by Code signatories. This should not be surprising since the DEXA service was launched six years ago, when the applicable Code was the 1998 Code. Pursuant to the 1998 Code, there was a requirement to train representatives on the technical aspects of the medicines they were promoting. The evidence from the 'DEXA placement in primary care' document previously provided to the Panel amply demonstrated that such technical training took place. There was no requirement under the 1998 Code, nor was there now, to preserve the evidence of such certification for more than three years. Therefore, it was particularly harsh that the Panel found Merck Sharp & Dohme in breach of the 2003 Code, which could not on any view have been the applicable Code for a service which began in 2000, and, in any event, for a failure to preserve training materials which, under any Code, were not required to be preserved for such a length of time.

Moreover, all of the representatives recently interviewed described training on the DEXA service in one form or another. Some thought there might have been a presentation at a regional meeting, others merely recalled this aspect being emphasised in informal mentoring by managers or other representatives. In any event, since the representatives had little to do with the service after providing the first contact details for the radiographers, it was not a difficult task needing constant reinforcement to separate the provision of the service from promotion. There was no opportunity to promote products once the service had been introduced. Recent interviewees confirmed this and also confirmed that they usually introduced the service in a separate non-promotional phase at the end of a promotional call, often in response to an unprompted observation from a GP about the lack of diagnostic facilities. In other cases, the representative might simply have noted an enquiry about the service and dropped the contact details off with the practice manager at another non-promotional visit. In some cases, the service was introduced after educational speaker meetings on osteoporosis and in others the coordination was provided by a secretary to the local consultant rheumatologist [sic] to whom the representative delivered details of radiographers available to provide screening.

Given employees' recollections that training had been given, Merck Sharp & Dohme submitted that, had it had an opportunity to submit its evidence on this point, the Panel could not have reached the conclusion that it did on the absence of evidence of training.

Merck Sharp & Dohme submitted that the Panel had misunderstood some of the materials submitted in its original response. The Panel's reference to the training slides in its ruling appeared to refer to the 'DEXA Placements DIY Guide', submitted in response to the complaint. Merck Sharp & Dohme accepted that these slides contained statements suggesting that surgeries were identified by sales data and that the representative might play a greater role in the service than any of its employees recalled was the case. However, the Panel was wrong to describe these as training materials. These were unauthorised documents produced in unclear circumstances by an unknown person or persons. No evidence was found that these materials were used in presentations or were otherwise used in training. They were disclosed as Merck Sharp & Dohme could not exclude the possibility that they were shown to a small number of representatives, and they were, therefore, responsive to the Panel's original request but it did not disclose them or describe them as training slides. In fact, the materials that Merck Sharp & Dohme produced and which clearly were representative training materials, specifically the Dexa Placement in Primary Care letter and the Forearm Bone Densitometry briefing document, made no such linkage. At least one of Merck Sharp & Dohme's recently interviewed representatives recalled representatives specifically being trained at a meeting using these slides.

Merck Sharp & Dohme was as certain as it could be that the 'DEXA Placement DIY Guide' was not used as formal training material and there was no evidence to the contrary. The Panel's ruling on that issue should not stand.

Failure to disclose Merck Sharp & Dohme's sponsorship on template letters was another issue that was not raised by the complainant. Merck Sharp & Dohme did not deny the findings of the Panel on this issue but it questioned whether this finding, on its own, would merit a ruling of a breach of Clause 18.1. It seemed very unlikely to justify a ruling of breach under Clauses 9.1 or 2.

The Panel did not make any rulings which upheld the complainant's allegations. The complainant made specific factual allegations relating to the forearm DEXA service offered to GPs by Merck Sharp & Dohme. Merck Sharp & Dohme had in its response effectively rebutted each element of the complaint. The specific factual allegations were that: representative colleagues employed within the FROSST division at the time had informed the group that they were required to manage this programme from start to end; sales metrics were considered when decisions were made regarding which practices

should be offered the scanners and representatives were required to input into the company's ETMS the number of patients that went on Merck's medicine Fosamax as a result of their scan.

Merck Sharp & Dohme had interviewed two representatives who had been on the FROSST team in 2000, when the service was introduced, and also the then national marketing manager and the then national sales manager. The evidence of all four employees, the two most senior of whom it had named, and on which it relied in its response to the complaint, unanimously rejected each allegation.

Merck Sharp & Dohme submitted that it had described in detail what role the representatives played in relation to the offer made to GPs. The offer was limited to just that, and Merck Sharp & Dohme noted that it was often made in response to an unsolicited enquiry from GPs lamenting the lack of osteoporosis diagnostic facilities in their, usually rural, practice areas. Merck Sharp & Dohme stated that it had found no evidence to support the allegations. Specifically, while representatives managed some of the administrative arrangements for the programme, the medical and technical aspects were left entirely to the radiographer.

Merck Sharp & Dohme noted that no documents were provided by the anonymous complainants to support their allegations, nor was it possible for the Authority to request further documents from them, either to support or undermine the allegations. Merck Sharp & Dohme provided examples of presentations made to representatives by managers, specifically the document 'DEXA Placement in Primary Care' and the document entitled 'Forearm Bone densitometry – briefing document'. The first document did not refer to any role to be played by the representative in relation to the service because all the representatives typically did was give the contact details of a radiographer to either the GP or practice manager and leave them to arrange suitable dates, times and lists of patients between them. The representatives would have checked, as a matter of courtesy, that the arrangements ran smoothly, but the evidence was that there was little more for them to do, once the service had been introduced. The 'Osteoporosis Audit and DEXA Scanning Programme' documents, which illustrated what happened at the individual practice level, supported this.

This was the best evidence available and was supported by evidence of five further representatives or former representatives involved in the offer of DEXA services and a manager, whom Merck Sharp & Dohme had now been able to identify and with whom it had spoken. Merck Sharp & Dohme offered to supply the names of all the representatives and managers it had interviewed, and, if necessary, the names of radiographers who provided the service and GPs who took it up. Merck Sharp & Dohme was confident that the evidence of its representatives was completely consistent. Merck Sharp & Dohme could not, therefore, see the basis upon which it could be said that the first allegation was proved, either on a balance of probabilities or beyond reasonable doubt. This conclusion was borne out by the fact that the Panel in its ruling made no finding of fact in relation to this allegation.

Merck Sharp & Dohme submitted that a similar pattern emerged when the second factual allegation was examined in relation to the evidence. The oral evidence of Merck Sharp & Dohme's employees supported its defence that sales metrics were not considered when decisions were made about where to place services. There was simply no evidence to the contrary, either documentary or oral testimony capable of being tested, on which the Panel could reach a different conclusion. Indeed, Merck Sharp & Dohme noted that the Panel had not made a ruling in relation to this allegation. Merck Sharp & Dohme explained in its response that in most cases there would be little or no prescribing of any osteoporosis treatments without a DEXA scanning facility because GPs were unable to reliably diagnose the condition.

Merck Sharp & Dohme submitted that the evidence considered by the Panel in relation to the third allegation was similarly uniformly in its favour. This allegation that data relating to sales generated by the DEXA service was entered onto the ETMS was entirely unsupported by documentary evidence or testable oral evidence. There appeared to be no field in the ETMS which such sales metrics could be entered. None of the employees interviewed recalled entering such data themselves and this was confirmed by recent interviews. Merck Sharp & Dohme had also identified some slides used for training representatives on the DEXA service in 2003 that described how information should be entered on the ETMS (copies of which were provided). Merck Sharp & Dohme noted that there was no reference to entering sales metrics. The credibility of the anonymous complainants must be seriously undermined by these findings. The Panel might already consider them to be less than reliable witnesses, their having mistaken the date the DEXA service started by two years. The anonymous complainants stated that the service began in 2002, when it in fact began in 2000, as was demonstrated by the documents referred to in the Panel's ruling, some of which dated from 2000 and 2001. At the very least this suggested that the complainants' informants (and it was clear that the complaint consisted essentially of anonymous second hand evidence not within the knowledge of the complainants) were not so closely involved in the DEXA service as to be properly aware of when it was introduced. There was no basis on which their evidence should be preferred to Merck Sharp & Dohme's evidence. The Panel had not made a ruling on the third allegation.

In summary, therefore, the great weight of evidence contradicted the anonymous allegations and, in any event, the Panel did not make a factual ruling in relation to any of the allegations. This could not lead to a finding of a breach of Clause 18.1.

The complainants' allegation of a breach of Clause 18.1 flowed directly from their three factual allegations and was dependent on their being made out, which they had not. This was demonstrated by the complainants' use of the word 'Accordingly …' to link the factual allegations and the aspect of the Code to which they stated the facts related.

Merck Sharp & Dohme submitted that at most, there was evidence that it had failed to disclose its

sponsorship on the template service letters, and that one, perhaps two, of its employees had created certain materials which, while not Code compliant, had little if any circulation within Merck Sharp & Dohme and were certainly not authorized by it. Neither set of facts appeared to fulfil the necessary elements of a breach of Clause 18.1, which was one of the most serious breaches of the Code. The Panel had not found that gifts, benefits in kind or pecuniary advantages had been offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend, buy or sell Fosamax. The DEXA service was a service to patients. It offered no advantage, pecuniary or otherwise to GPs or their staff and was not promotional either in conception or delivery. The breaches ruled by the Panel in relation to the absence of logos and absence of evidence of training materials on the need to distinguish between promotion and the provision of services did not appear to justify a breach of Clause 18.1, particularly when evidence of its employees rebuted the presumption that, because no written materials could be produced from over three years ago, no training had taken place.

If the elements of a breach of Clause 18.1 of the 2003 Code were not made out then it must follow that there could have been no breach of Clauses 2 or 9.1. Even if the failure to produce evidence of written training materials and to include a logo on the patient letter was a breach of Clause 18.1, Merck Sharp & Dohme questioned whether these were sufficiently grave to justify rulings of a breach of Clauses 9.1 and 2. Merck Sharp & Dohme also asked whether an isolated disclosure of one unauthorised set of slides dating from over 5 years ago, whose authorship and provenance could not be precisely determined, that might, at most, have been seen by a handful of representatives whose subsequent oral evidence was that they did not lead to their linking the provision of the service with promotion of Fosamax, should lead to a ruling of a breach of Clause 2, when all the other evidence pointed to Merck Sharp & Dohme's official training on the programme and delivery of it having been Code compliant.

In the light of its submissions Merck Sharp & Dohme concluded that: it was clear on the face of the ruling that the factual allegations in the complaint were not made out; an adverse ruling had been made by the Panel in relation to alleged breaches which were not put to Merck Sharp & Dohme; the wrong version of Code had been used to justify a finding of breach and the finding of breach appeared to relate to an inability to produce documentary evidence of appropriate training from six years ago, when no version of the Code required training material to kept for more than three years.

Merck Sharp & Dohme thus submitted that the Panel's ruling in relation to breaches of Clauses 2, 9.1 and 18.1 of the 2003 edition of the Code should be set aside by the Appeal Board.

APPEAL BOARD RULING

The Appeal Board noted Merck Sharp & Dohme's submission that the purpose of the DEXA programme was to expand the diagnosed population of osteoporotic patients. The programme had started to wind down in the latter half of 2003 and so no new representatives were trained from this point; only those already trained and experienced on the programme continued to work on it. Managers had continued to provide some training by mentoring in the field. Merck Sharp & Dohme's representative explained that this was one of the reasons for the lack of available training documentation concerning the DEXA programme. Nonetheless, the Appeal Board considered that the company should have been able to produce job bags for the relevant training material which governed the representatives' activities from the latter part of 2003 onwards.

The Appeal Board noted that the company was able to provide little evidence about the provenance, status and use of the 'DEXA Placements DIY Guide' and the 'DEXA checklists' which it submitted were found on the computer of an existing employee who had worked on the DEXA programme. That employee did not write either document. The Appeal Board was alarmed at the 'DEXA Placements DIY Guide' and concerned that anyone could have produced it. The company's investigation indicated that the 'Guide' had been discussed at a best practice meeting typically attended by one representative from each of the six sales regions and four regional managers. The basis of the discussion and its outcome were not known. There was no evidence that the material had formed part of any representatives' training for the DEXA service. The Appeal Board considered that there was no evidence on the balance of probabilities that the material had been used to train representatives or had otherwise been disseminated beyond the meeting; or to indicate that it had otherwise influenced the behaviour of representatives in the field.

The Appeal Board further noted another document 'Guide to Proposal Development' which related to funding for osteoporosis selective case finding in primary care. Under a heading of 'Benefits of the project' was stated 'Environment positive for Fosamax with high market share in locality and inclusion in clinical guidelines'. The Appeal Board was concerned at this statement but noted that Merck Sharp & Dohme's representatives stated that to the best of their knowledge no proposals had ever taken place, nor was there any evidence that the document had influenced representatives' behaviour.

The Appeal Board understood why the Panel was concerned about the material. However, it considered that the complaint had not established on the balance of probabilities that the arrangements amounted to a breach of Clause 18.1 of the Code. Thus the Appeal Board ruled no breach of Clause 18.1 and hence no breach of Clauses 9.1 and 2.

The Appeal Board noted the Panel's report in accordance with Paragraph 8.2 of the Constitution and Procedure. The Appeal Board noted its comments above and its rulings of no breach of the Code. The Appeal Board decided to take no further action.

Complaint received **30 June 2006**

Case completed **22 November 2006**

CASE AUTH/1862/7/06

PROSTRAKAN/DIRECTOR v SHIRE

Breach of undertaking

ProStrakan complained that promotional materials for Calcichew-D_3 Forte (calcium carbonate and colecalciferol) issued by Shire were in breach of the undertaking and assurance given in Case AUTH/1825/4/06. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the Authority's responsibility to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

In Case AUTH/1825/4/06 the claim 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 was preferred over Adcal-D_3 by 80% of patients', which was referenced to Rees and Howe (2001), was ruled to be misleading in breach of the Code. The resultant form of undertaking and assurance, signed on 5 June, indicated that the claim had last been used on 6 April.

ProStrakan alleged however, that the claim at issue was continuing to be used in a journal advertisement, an advertisement on exhibition panels and a leavepiece.

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

The journal advertisement which had appeared in Pulse, 22 June, featured the claim 'She should appreciate a Ten Second chew of Calcichew-D_3 Forte. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients'.

The Panel considered that the advertisement was caught by the undertaking given in Case AUTH/1825/4/06 in that there was insufficient detail about why patients preferred Calcichew-D_3 Forte to Adcal-D_3. The undertaking in the previous case had been signed on 5 June. Due to lead times at the publishers, Shire was unable to cancel the booking. Shire had thus taken steps to comply with its undertaking; publication of the advertisement on 22 June was due to circumstances beyond its control. No breach of the Code was ruled.

An exhibition panel used at a meeting (25-28 June) featured the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients' below which was a brief description of the study by Rees and Howe and a list of the reasons as to why Calcichew-D_3 Forte was preferred (easier to chew/swallow and less chalky/gritty/sticky). Similarly, two leavepieces stated the reasons for preference. The Panel considered that these materials complied with the undertaking previously given and no breach of the Code was ruled which was upheld on appeal by ProStrakan.

With regard to a third leavepiece the Panel noted that although it contained the claim 'Calcichew-D_3 Forte is preferred by 80% of patients (n=94) to Adcal-D_3' there was no indication as to why a preference had been expressed. The Panel noted that Shire was in the process of withdrawing the piece because of an unrelated claim. In the Panel's view, however, the leavepiece should have been withdrawn pursuant to the undertaking given in Case AUTH/1825/4/06. Shire had breached its undertaking and high standards had not been maintained and breaches of the Code were ruled. Inadequate action leading to a breach of undertaking was an activity likely to bring discredit to, and reduce confidence in, the industry. A breach of Clause 2 was ruled. These rulings were upheld on appeal by Shire.

ProStrakan Pharmaceuticals complained that promotional materials for Calcichew-D_3 Forte (calcium carbonate and colecalciferol) issued by Shire Pharmaceuticals Ltd were in breach of the undertaking and assurance given in Case AUTH/1825/4/06. The materials in question were a journal advertisement (ref 003/0471), a leavepiece (ref 003/0458) and exhibition panels from the National Osteoporosis Society Annual Meeting. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

In Case AUTH/1825/4/06 ProStrakan had alleged that the claim 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 was preferred over Adcal-D_3 by 80% of patients', which was referenced to Rees and Howe (2001), was misleading. The Panel subsequently ruled the claim in breach of the Code as alleged. The resultant form of undertaking and assurance, signed on 5 June 2006, indicated that use of the claim would cease forthwith and that the advertisement in which it had appeared had last been used on 6 April 2006.

ProStrakan marketed Adcal-D_3 (calcium carbonate and colecalciferol). Both Calcichew-D_3 Forte and Adcal-D_3 were tablets for chewing.

COMPLAINT

ProStrakan noted that there were two instances where the claim at issue was continuing to be used: an advertisement in Pulse, 22 June 2006, where the lead time for this journal was nine days; National Osteoporosis Society Annual Meeting exhibition panels and a leavepiece (ref 003/0458) found on the stand and which was part of a series of leavepieces (ref 003/0446 and ref 003/0456).

ProStrakan alleged that its additional concern was the system of disregard of the Panel's ruling and the implied significant lack of process and oversight in Shire's internal procedures.

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

RESPONSE

Shire strongly refuted the statement by ProStrakan alleging 'the system of disregard of the Panel's ruling and the implied significant lack of process and oversight in Shire's internal procedures'.

Shire submitted that prior to the ruling in Case AUTH/1825/4/06, following discussions with ProStrakan, it had withdrawn and modified the advertisements at issue on 31 March 2006. Further, following the Panel's ruling and Shire's undertaking of 5 June 2006, it promptly withdrew the modified advertisements from circulation. Due to print deadlines, publication of the withdrawn advertisements could not be effected immediately. Copies of letters from publishers dated 5 June onwards to confirm Shire's prompt action were provided. In particular a letter of 5 June referred to publication of the advertisement in the 22 June edition of Pulse. The advertisement was withdrawn from the 29 June edition. Shire therefore firmly denied that it was in breach of its undertaking.

Shire submitted that ProStrakan had written to it regarding the 22 June Pulse advertisement on 23 June but did not await Shire's response before complaining to the Authority. With regard to the Panel's ruling in Case AUTH/1825/4/06, Shire noted that the Panel had stated 'Both products had similar indications and although they [Calcichew-D_3 Forte and Adcal-D_3] had different constituents the Panel considered that it was not unreasonable to compare the two' and 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients' was misleading, in breach of Clauses 7.2 and 7.3 of the Code as it was not specified as to why there was a preference and it might imply that taste was the reason for 80% of the patients preferring Calcichew-D_3 Forte over Adcal-D_3.

Shire emphasised again that it had modified the above claim before the original complaint by ProStrakan to the Authority, by omitting the phrase 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise'. The offending material was withdrawn on 31 March 2006.

Shire submitted it had interpreted the qualification in the ruling as meaning that a comparison from this publication could be used, provided that the preferential advantages of Calcichew-D_3 Forte over Adcal-D_3 were clearly listed, thereby ensuring that the comparison would not be misleading.

Shire reviewed its materials and decided that the exhibition panel (ref 003/0442d) and leavepieces (refs 003/0446, 003/0456, 003/0457) were permissible and not misleading because they did not imply that taste was the reason why 80% of patients preferred Calcichew-D_3 Forte over Adcal-D_3. Preferential palatability advantages from Rees and Howe were clearly listed. Results from the one parameter measured (taste), which did not translate into 'good' or 'bad' on the opposite ends of the visual analogue scale (ie 'very sweet' or 'very bitter') and which did not show a significant difference between products, were not quoted.

Shire noted the exhibition panel carried the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients'. It did not include the claim 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise', or similar, against which the Panel had ruled. Further, preferential palatability advantages from Rees and Howe were clearly listed. Nonetheless to avoid further altercations, Shire had promptly removed the exhibition panel at ProStrakan's request.

Shire noted that one copy of the leavepiece (ref 003/0458) was on at its stand. In Shire's regular review of materials this leavepiece was scheduled to be withdrawn as it contained the claim: 'Calcichew-D_3 Forte. Now in a new monthly pack'. As the pack would have been issued one calendar year in July 2006 Shire could no longer state that the pack size was new.

Shire submitted that this leavepiece was modified in April 2006 following Prostrakan's initial complaint to Shire. It was not intended to be used at the National Osteoporosis Society meeting as it was in the process of being withdrawn, for the reason given above. It contained the claim 'Calcichew-D_3 Forte is preferred by 80% of patients (n=94) to Adcal-D_3' but had not qualified the reasons (various aspects of palatability) why there was a preference. It did not incorporate the claim 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise', or similar, against which the Panel had ruled. Shire submitted that the claim did not imply that taste was the main reason for the preference – but rather that the overall impression from the respective chewable tablets was the reason for the preference. The detailed significant reasons for the preference were given in Rees and Howe.

Shire submitted that when the leavepiece was discovered on the stand and pointed out by ProStrakan it was removed immediately as it was clear that an error had occurred in it being sent to the meeting as current material. Shire accepted that this was an error on its part and that this leavepiece should not have been on the stand. Since the meeting Shire had ensured that its printers had destroyed all remaining copies of this leavepiece and that all members of the sales force had destroyed any copies that might have still been in circulation.

Shire noted that at the meeting ProStrakan had drawn its attention to the presence of this single leavepiece and was satisfied with its action stated above. ProStrakan had agreed not to take the matter further if Shire complied with its request – which it did. It was not necessary to refer this matter to the Authority.

Shire submitted that it was not in breach of Clauses 22, 9.1 or 2 and it had taken all steps to comply with the Panel's ruling.

PANEL RULING

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

The Panel noted that the advertisement which had appeared in Pulse, 22 June, featured the claim 'She

should appreciate a Ten Second chew of Calcichew-D_3 Forte. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients'.

The Panel considered that the advertisement was caught by the undertaking given in Case AUTH/1825/4/06 in that, as with the claim previously at issue 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', there was insufficient detail about why patients preferred Calcichew-D_3 Forte to Adcal-D_3. The undertaking in the previous case had been signed on 5 June 2006; the advertisement at issue was published in Pulse on 22 June. A letter from the publishers, dated 5 June, showed that Shire had tried to cancel bookings for Calcichew advertisements in the June 8, 15 and 22 issues of Pulse but that this had not been possible. The publishers were able to cancel the booking for June 29. The Panel thus noted that Shire had taken steps to comply with its undertaking; publication of the advertisement on June 22 was due to the lead time at the publishers and thus beyond Shire's control. The Panel considered that Shire had complied with its undertaking and so no breach of Clauses 2, 9.1 and 22 was ruled.

The Panel noted that one of the exhibition panels used at the meeting of the National Osteoporosis Society (25-28 June 2006) featured the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients' below which was a brief description of the study by Rees and Howe and a list of the reasons as to why Calcichew-D_3 Forte was preferred (easier to chew/swallow and less chalky/gritty/sticky). Similarly, two of the leavepieces (refs 003/0446 and 003/0456) stated the reasons for preference. The Panel considered that these materials complied with the undertaking previously given and no breach of Clauses 2, 9.1 and 22 was ruled. The ruling of no breach of Clause 22 was appealed by ProStrakan.

With regard to a third leavepiece (ref 003/0458) the Panel noted that although it contained the claim 'Calcichew-D_3 Forte is preferred by 80% of patients (n=94) to Adcal-D_3' there was no indication as to why a preference had been expressed. The Panel noted that Shire was in the process of withdrawing the piece because of the claim 'Now in a new monthly pack'. In the Panel's view, however, the leavepiece should have been withdrawn pursuant to the undertaking given in Case AUTH/1825/4/06. The leavepiece had been used almost three weeks after the undertaking had been signed. The Panel considered that Shire had thus breached its undertaking. A breach of Clause 22 was ruled. High standards had not been maintained and so a breach of Clause 9.1 was ruled. These rulings were appealed by Shire.

The Panel noted that the supplementary information to Clause 2 stated that inadequate action leading to a breach of undertaking was an activity likely to bring discredit to, and reduce confidence in, the industry. A breach of Clause 2 was ruled. This ruling was appealed by Shire.

APPEAL BY PROSTRAKAN

ProStrakan appealed the ruling of no breach of Clause 22 with regard to the material used at the National Osteoporosis Society meeting. ProStrakan alleged that Shire had not complied with the letter or the spirit of the ruling in Case AUTH/1825/4/06 and that the comparison between two products with different constituents and clearly identified differences in efficacy was unfair and misleading.

ProStrakan noted the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients' was supplemented with reasons why Calcichew-D_3 Forte was preferred (easier to chew/swallow and less chalky/gritty/sticky). This claim was used in exhibition panels and two leavepieces, 003/0446 and 003/0456. This claim was ruled not in breach of the Clauses 2, 9.1 and 22.

ProStrakan noted that the claim at issue in Case AUTH/1825/4/06 was 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise. In a comparative study, Calcichew-D_3 Forte was preferred over Adcal-D_3 by 80% of patients', referenced to Rees and Howe. The amended claim did not comply with the previous ruling.

ProStrakan noted the original reason for complaint was that this comparison was unfair and misleading, as Adcal-D_3 had 250mg of calcium carbonate more per tablet than Calcichew-D_3 Forte and these products were being compared as equivalent. The implication of equivalence was especially misleading as the clinical efficacy data differences for the doses of elemental calcium were very different. This was clearly shown in Section 5.1 of the summaries of product characteristics (SPCs) of both products.

ProStrakan noted from the Adcal-D_3 SPC that there was strong evidence that supplemental calcium and vitamin D_3 could reduce the incidence of hip and other non-vertebral fractures. In a randomised, placebo controlled study, 3,270 patients treated with 1200mg elemental calcium and 800 IU vitamin D_3 daily, ie the same dose delivered by two tablets of Adcal-D_3, the number of hip fractures was 43% lower (p=0.043) and the total number of non-vertebral fractures was 32% lower than among those who received placebo. A positive effect on bone mineral density was also observed.

ProStrakan noted that the SPC for Calcichew-D_3 Forte contained the same data stating the important dose as 1200mg/day of elemental calcium. Calcichew-D_3 Forte was a chewable tablet containing 1250mg calcium carbonate (equivalent to 500mg of elemental calcium) plus 400 IU vitamin D_3 taken twice daily.

ProStrakan noted from the Adcal-D_3 SPC that it was a chewable tablet containing 1500mg calcium carbonate PhEur (equivalent to 600mg of elemental calcium) plus 400 IU colecalciferol (vitamin D_3).

ProStrakan submitted that it had provided a more detailed review of all the relevant data in its complaint in Case AUTH/1825/4/06. There were three elements of comment within the Panel's ruling:

- The Panel had considered that the patients' views on these other parameters (grittiness, chalkiness, taste (bitter or sweet), ease of chewing, ease of swallowing and stickiness of each product) had influenced their preference given that there was no

difference between the two as to perception of taste.

- The Panel was concerned that insufficient detail was given about what it was that patients preferred about treatment with Calcichew-D_3 Forte compared to treatment with Adcal-D_3. The claim implied that not only did patients prefer Calcichew-D_3 Forte to Adcal-D_3 but they also found it pleasant to take. There was no data in that regard.
- The Panel had disagreed with Shire's view that the data on efficacy evaluations and health economics were irrelevant to the current complaint which only dealt with the issue of patient preference. The Panel considered that in addition to palatability a patient's knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products might affect their preference for one or the other. Without such knowledge patients would be unable to express a genuine, well-informed preference.

ProStrakan submitted that the ruling identified the need to be more explicit about preference with regard to grittiness, chalkiness, etc, however, Rees and Howe did not provide the patient with any understanding and 'knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products', therefore, 'Without such knowledge patients would be unable to express a genuine, well-informed preference'. ProStrakan submitted the claim used to imply preference of Calcichew-D_3 Forte to Adcal-D_3 was therefore fundamentally flawed:

- The study compared products of significantly different doses.
- The doses had very different evidence-bases.
- There was no explanation to patients regarding the evidence-based differences therefore patients were unable to express a genuine, well-informed preference.

ProStrakan alleged that the continued use of the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients', was in breach of the original ruling and was still misleading and unfair with or without issues about grittiness, chalkiness etc added.

COMMENTS FROM SHIRE

Shire did not consider that the claims at issue were unfair or misleading. The revised claim used in the exhibition panel and related items strongly implied greater acceptability, with its elements clearly defined (ie ease of chewing, ease of swallowing, chalkiness, grittiness and stickiness) as the observed reasons for preference. Rees and Howe compared acceptability, with no reference to efficacy. Efficacy was not an issue in this claim for the reasons given above. Further, patients were very unlikely to be aware of any differences between products (if they existed) in efficacy for their chronic condition. In any event, the assertion by ProStrakan that treatment with Adcal-D_3 (600mg calcium plus 400 IU vitamin D_3) led to significantly greater efficacy than with Calcichew-D_3 Forte (500mg calcium plus 400 IU vitamin D_3) was inconsistent with overall published data on the relevant calcium/vitamin D medications. There were no published clinical data for Adcal-D_3 apart from Rees and Howe.

FURTHER COMMENTS FROM PROSTRAKAN

ProStrakan stated that it had consistently represented its arguments which established the initial case for the ruling of a breach of the Code in Case AUTH/1825/4/06. The activities and promotion of the study by Rees and Howe, continued to be unfair and misleading.

APPEAL BOARD RULING

The Appeal Board noted that the claims at issue were different to those considered in Case AUTH/1825/4/06 as the parameters used to measure patient preference were clearly stated; easier to chew/swallow and less chalky/gritty/sticky. The Appeal Board considered that these materials thus complied with the undertaking previously given and the Appeal Board upheld the Panel's ruling of no breach of Clauses 2, 9.1 and 22.

APPEAL BY SHIRE

Shire appealed the Panel's rulings of breaches of Clauses 2, 9.1 and 22 with regard to the leavepiece (ref 003/0458). Shire submitted that the leavepiece found at its stand at the meeting did not breach the undertaking because it was not similar to the advertisements ruled in breach by the Panel in Case AUTH/1825/4/06 because:

- The claim in the leavepiece was substantially shorter than that in the advertisement, with a significant amount of text having been removed which the Panel had ruled overall to be misleading. The leavepiece did not incorporate the claim 'Chew Calcichew-D_3 Forte for Ten Seconds for a pleasant surprise', or similar, against which the Panel had ruled.
- This shortened claim in the leavepiece, 'Calcichew-D_3 Forte is preferred by 80% of patients (n=94) to Adcal-D_3' was not misleading in its presented context.

Shire submitted that it followed from its reasons given above that high standards had been maintained and the leavepiece was therefore not in breach of Clause 9.1.

Shire noted that the leavepiece was scheduled to be withdrawn from use for a separate reason and should not have been on the exhibition stand.

Shire submitted that there was no breach of Clause 2, since its actions had not brought discredit on, or reduced confidence in, the pharmaceutical industry. In particular Shire took great care at the conference to minimise open confrontation with ProStrakan that might well have reduced confidence in the industry. There was ample evidence that Shire had endeavoured to comply throughout with the ruling in Case AUTH/1825/4/06.

Shire submitted that it was not in breach of Clauses 2, 9.1 or 22 and it had taken all steps to comply with the ruling.

COMMENTS FROM PROSTRAKAN

ProStrakan stated that the Panel's ruling in Case AUTH/1825/4/06 should be the basis of the appeal. The study and the claims arising from it were unfair and misleading.

ProStrakan noted three elements of comment within the ruling in Case AUTH/1825/4/06. The Panel had considered that the patients' view on these other parameters (grittiness, chalkiness, taste (bitter or sweet), ease of chewing, ease of swallowing and stickiness of each product) had influenced their preference given that there was no difference between the two as to perception of taste. The Panel was concerned that insufficient detail was given about what it was that patients preferred about treatment with Calcichew-D_3 Forte compared to treatment with Adcal-D_3. The claim implied that not only did patients prefer Calcichew-D_3 Forte to Adcal-D_3 but they also found it pleasant to take. There was no data in that regard. The Panel had disagreed with Shire's view that the data on efficacy evaluations and health economics were irrelevant to the current complaint which only dealt with the issue of patient preference. The Panel considered that in addition to palatability a patient's knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products might affect their preference for one or the other. Without such knowledge patients would be unable to express a genuine, well informed preference.

ProStrakan submitted that the ruling identified the need to be more explicit about preference with regard to grittiness, chalkiness etc, however Rees and Howe did not provide the patient with any understanding and 'knowledge of some of the efficacy evaluations and differences in clinical outcomes between two products', therefore, 'without such knowledge patients would be unable to express a genuine, well informed preference'. ProStrakan alleged that the claim used to imply preference of Calcichew-D_3 Forte to Adcal-D_3 was therefore fundamentally flawed:

- The study compared products of significantly different doses.
- The doses had very different evidence-bases.
- There was no explanation to patients regarding the evidence-based differences therefore, patients were unable to express a genuine, well informed preference.

ProStrakan submitted that the continued use of the claim 'Calcichew-D_3 Forte. Preferred to Adcal-D_3 by 80% of patients' was in breach of the original ruling and was still misleading and unfair with or without issues re grittiness, chalkiness etc added.

APPEAL BOARD RULING

The Appeal Board noted that the leavepiece at issue (ref 003/0458) featured the claim 'Calcichew-D_3 Forte is preferred by 80% of patients (n=94) to Adcal-D_3'. There was, however, no indication as to why such a preference had been expressed.

The Appeal Board considered that the claim at issue was closely similar to that at issue in Case AUTH/1825/4/06 and thus the leavepiece should have been withdrawn pursuant to the undertaking given in that case. Shire had thus breached its undertaking and the Appeal Board upheld the Panel's ruling of a breach of Clause 22. High standards had not been maintained and the Appeal Board thus upheld the Panel's ruling of a breach of Clause 9.1. The appeal on these points was unsuccessful.

The Appeal Board noted that the supplementary information to Clause 2 stated that inadequate action leading to a breach of undertaking was an activity likely to bring discredit upon, and reduce confidence in, the pharmaceutical industry. The Appeal Board thus upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **29 June 2006**

Case completed **15 December 2006**

CASE AUTH/1870/7/06

AMGEN v ROCHE

Promotion of NeoRecormon

Amgen complained about an exhibition panel, a brochure and slides which Roche had used to promote NeoRecormon (epoetin beta) at the European Dialysis and Transplant Association Congress in July 2006. The materials at issue referred to a poster presentation, Goldsmith *et al* (2005). Amgen supplied Aranesp (darbepoetin alfa).

The claim 'In a retrospective study, a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alpha SC' appeared on the exhibition panel. Dose reduction claims were also referred to in a slide which featured a bar chart headed 'Route of Administration Dose Saving with Epoetin ß SC vs IV' and depicted the percentage dose saving of subcutaneous (SC) vs intravenous (IV) administration as 33% at 7-12 months and 19% at 1-6 months.

Amgen alleged that the claim that 'a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alfa SC' did not represent the available data and was neither fair nor balanced. Goldsmith *et al* was not a prospective head-to-head-study, it was a retrospective analysis that had not been peer reviewed nor had it subsequently been published in a peer-review journal. Imbalances between patient groups could not be excluded as this was not a randomised study, distribution of brands between countries differed and the study design did not ensure similar evaluation periods.

In contrast Amgen submitted that Tolman *et al* (2005) was a well designed, prospective, randomised study which evaluated the doses of NeoRecormon and Aranesp needed to maintain stable haemoglobin. 162 unselected haemodialysis patients were converted from thrice-weekly SC NeoRecormon to a weekly administration of Aranesp (n=81) or NeoRecormon (n=81). After 9 months, the difference in haemoglobin level and dose between the two treatment arms was measured. The study showed that to maintain haemoglobin levels, a significantly higher dose of NeoRecormon than Aranesp was required ($p<0.001$). The mean dose of NeoRecormon was 44% higher than the dose of Aranesp at the end of the study. These results clearly contradicted Goldsmith *et al*.

The Panel noted that the exhibition panel was headed 'NeoRecormon', followed by 'Energy to make a difference. NeoRecormon SC is a cost efficient option for treatment of anaemia'. The claim at issue 'In a retrospective study, a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alfa SC', was referenced to the Revised European Best Practice Guidelines 2004 (EBPG) and appeared as a bullet point immediately above a table, referenced to Goldsmith *et al*, which compared the mean weekly IV and SC doses of NeoRecormon and darbepoetin alfa.

The Panel noted that Goldsmith *et al* was a retrospective analysis which assessed anaemia management and current treatment practices with erythropoietins in patients on haemodialysis with particular emphasis on the impact that different erythropoietins and their routes of administration had on haemoglobin (Hb) control. Mean Hb levels were similar between the three cohorts: NeoRecormon, darbepoetin alfa and epoetin alfa. Hb control was defined as the proportion of Hb values within the target range of 10-12g/dl. Mean weekly SC doses for darbepoetin alfa and for epoetin beta were 10,210 IU and 7,890 IU respectively. A 24% dose reduction was possible with SC epoetin beta vs SC darbepoetin alfa.

Tolman *et al* was an open label, prospective, randomized, 9 month study which compared the clinical effectiveness of SC weekly NeoRecormon and darbepoetin alfa on conversion from thrice weekly SC NeoRecormon. There was no control group. Patients were managed according to their Hb levels. Over the course of the study maintenance of Hb levels was associated with a need to increase NeoRecormon doses whilst darbepoetin alfa doses fell. The Hb target range was 11-12g/dl. The mean weekly epoetin beta dose at 9 months was 44% higher than the mean darbepoetin alfa dose (133 IU/kg vs 92 IU/kg). The authors noted that they had failed to observe complete dose and Hb stabilization in both arms until at least week 28 after conversion.

The Panel noted that Roche had referred to a number of other studies which it considered supported its claim eg Locatelli *et al* (2003), Locatelli *et al* (2001) and Vanrenterghem *et al*. Although these studies showed that lower doses of SC epoetin beta were required than SC darbepoetin the differences between the two were less than the 24% reported by Goldsmith *et al* and ranged from 12.3% to 16.4%. Locatelli *et al* (2003) reported that the dose increase seen in patients on darbepoetin appeared to be due to the fact that they had been sub-optimally controlled whilst on SC epoetin. The studies all differed in the Hb targets which they set.

Overall the Panel considered that the data was such that the claim at issue was an oversimplification of the situation and thus did not represent the balance of the evidence. The claim was misleading as alleged. A breach of the Code was ruled.

The Panel noted that the slide depicting the bar chart entitled 'Route of Administration Dose Saving with Epoetin ß SC vs IV' was referenced to data on file and made no comparison with darbepoetin alfa. The subsequent bar chart compared the achievement of Hb target range of all erythropoietin stimulating agents (ESAs). The Panel did not know how the slide was presented at the symposium. On the evidence before it the Panel did not consider the slide constituted a misleading comparison with darbepoetin alfa and thus on this narrow point considered that it was not misleading as alleged.

The slide was also reproduced in the brochure alongside the abstract entitled 'Hb Control: Current Clinical Practice'. The Panel did not consider that it invited a comparison with darbepoetin alfa as alleged and on this narrow point no breach of the Code was ruled.

With regard to target haemoglobin levels Amgen noted that a Roche exhibition panel headed 'NeoRecormon achieves Hb stability in practice' featured the claims 'In a retrospective study (n=1098) NeoRecormon SC controls Hb levels within a 10-12g/dl range in 75% of haemodialysis patients' and 'Significantly more haemodialysis patients treated with NeoRecormon achieve constant Hb control within a 10-12g/dl range compared with darbepoetin alfa'. The claims were referenced to Goldsmith *et al*.

Furthermore, in connection with a Roche sponsored satellite symposium entitled 'Anaemia Management : from Targets to Reality', Roche distributed a brochure which included a bar chart based on Goldsmith *et al*. The bar chart was headed 'Staying Within Hb Target Range. Are all ESAs Equal' which Amgen stated purportedly showed that Aranesp enabled fewer patients to reach the Hb target range of 10-12g/dl than NeoRecormon.

Amgen alleged that Roche's claims were misleading in their treatment of target haemoglobin levels. Specifically, the target haemoglobin level (10-12g/dl) used in Goldsmith *et al* did not have real clinical relevance and was inconsistent with the EBPG recommendation that, in general, patients with chronic kidney disease should maintain a target haemoglobin concentration of > 11g/dl. ESAs should be given to all chronic kidney disease patients with haemoglobin levels consistently < 11g/dl where all other causes of anaemia had been excluded.

Also in the brochure, a haemoglobin level of ≥ 11g/dl was said to be 'recommended'. Applying the EBPG, it could be seen, even with Goldsmith at al, that more patients achieved the target level with Aranesp than with NeoRecormon: 58% of Aranesp patients reached Hb > 11g/dl, whereas only 46% of NeoRecormon patients achieved such levels.

The failure to draw readers' attention either in the exhibition panel or the brochure to the fact that Goldsmith *et al* was not consistent with the EBPG was alleged to be a distortion and directly misled the audience by undue emphasis. The material was not sufficiently complete to enable the reader to form their own opinion of the therapeutic value of the medicine.

The Panel noted that the EBPG discussed haemoglobin targets for anaemia treatment: this was dependent upon patient population and was recommended in general to be >11g/dl. Goldsmith *et al* stated that Hb control was defined as the proportion of the Hb values within the target range of 10-12g/dl during the 12 month study period. This range reflected current licences and was based on reports relating to clinical outcomes to provide acceptable variability (±1g/dl) around the EBPG Hb target of 11g/dl. The Panel noted Amgen's submission that if the EBPG were applied to Goldsmith *et al* more patients achieved the target level with darbepoetin alfa than with NeoRecormon; 58% of darbepoetin alpha patients reached Hb > 11g/dl compared to 46% of NeoRecormon.

The Panel considered that the exhibition panel was not sufficiently complete to enable the reader to form their own opinion of the therapeutic value of the medicine as alleged. The EBPG recommended target was not mentioned. A breach of the Code was ruled.

In relation to the brochure the Panel noted that the bar chart at issue depicting data from Goldsmith *et al* accompanied an abstract headed 'Hb Control: Current Clinical Practice'. The abstract began by stating 'International studies and registry data have shown consistent improvement in the management of CKD [chronic kidney disease] related anaemia, with an increasing proportion of patients achieving recommended Hb levels ≥ 11g/dl with erythropoiesis stimulating agents (ESAs)'.

The accompanying bar chart depicting the results of Goldsmith *et al*, however, referred to an Hb target range of 10-12g/dl and showed that more patients hit this range with NeoRecormon than darbepoetin alpha. The Panel considered that to refer to one target level in the text but to depict results relating to another was inconsistent and thus misleading. A breach of the Code was ruled.

Amgen alleged that the statement 'Guidelines favour SC administration for both clinical and economic reasons' referenced to EBPG was misleading. The EBPG only made such a statement regarding epoetin alfa [sic] (NeoRecormon) and only in CKD patients not undergoing dialysis and in transplant patients.

Moreover by placing this statement directly under the comparison with darbepoetin alfa regarding dose requirements via the SC route of administration, this amounted to a claim relying on an implicit comparison with Aranesp which was misleading and incapable of substantiation. The relevant parts of the EBPG were referred to. The statement that SC was recommended for economic and practical reasons was only true and capable of substantiation for epoetin alfa and epoetin beta. It was not true or capable of substantiation for darbepoetin alfa; IV darbepoetin alfa was as cost efficient as SC administration. Accordingly, the EBPG specifically pointed out that darbepoetin alfa, in contrast to NeoRecormon, could be administered either IV or SC without dose adjustments. Again this directly relevant fact was absent on the exhibition panel.

The Panel noted that the claim at issue appeared on the same exhibition panel as the comparative bullet point in the first point above and immediately beneath a table comparing the mean weekly SC and IV dose of NeoRecormon and darbepoetin alfa. The exhibition panel also featured some claims which were clearly only about NeoRecormon. Given the context in which it appeared it was unclear as to whether the claim 'Guidelines favour SC administration for both clinical and economic reasons' related only to NeoRecormon or was a comparison of NeoRecormon with darbepoetin alfa.

The Panel noted that the the EBPG read 'The recommended route of administration is dependent on the patient group being treated and the type of ESA used'. The Panel noted the economic, clinical

and practical points listed in relation to the route of administration and choice of epoetin for each patient group. Economic reasons were mentioned in relation to NeoRecormon SC for patients on dialysis, CKD patients not undergoing dialysis and in transplant patients. A table summarizing the recommendations gave SC administration as the recommended route for all patient types.

The guidelines stated that darbepoetin alfa could be given either IV or SC without dose adjustment in all CKD patients. In haemodialysis patients, darbepoetin alfa might be easier to administer IV but the SC rate was preferable in all other CKD patients. Given that there was no dose difference between IV and SC darbepoetin there was no economic reason to use the SC route. The Panel considered that given the context in which it appeared, the claim 'Guidelines favour SC administration for both clinical and economic reasons' was misleading about the guidelines' recommendations for darbepoetin alfa and not capable of substantiation in this regard. Breaches of the Code were ruled.

Amgen Limited complained about the promotion of NeoRecormon (epoetin beta) by Roche Products Limited. The materials at issue referred to a poster presentation, Goldsmith *et al* (2005), and comprised an exhibition panel, a brochure and slides which had been used by Roche at the European Dialysis and Transplant Association Congress in Glasgow, 15-17 July. Amgen supplied Aranesp (darbepoetin alfa).

1 Claim 'In a retrospective study, a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alpha SC'

This claim appeared on Roche's exhibition panel. Dose reduction claims were also referred to in a slide presentation the relevant part of which was subsequently circulated by Roche as part of a brochure at the Congress. The slide at issue featured a bar chart headed 'Route of Administration Dose Saving with Epoetin ß SC vs IV' and depicted the percentage dose saving of subcutaneous (SC) vs intravenous (IV) administration as 33% at 7-12 months and 19% at 1-6 months.

COMPLAINT

Amgen alleged that the claim that 'a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alfa SC' did not represent the current state of scientific research and available data. The supporting reference Goldsmith *et al* did not describe a prospective head-to-head-study, which would be the only valid evidence for the claimed advantages of NeoRecormon towards Aranesp. Goldsmith *et al*, a poster displayed at the American Society of Nephrology in November 2005, was a retrospective analysis which had not been peer reviewed, nor had it subsequently been published in a peer-review journal. Imbalances between patient groups could not be excluded as this was not a randomised study, distribution of brands between countries differed and the study design did not ensure similar evaluation periods between brands.

To comply with the Code promotional material must be accurate, balanced, fair and unambiguous and based on an up-to-date evaluation of all the evidence and reflect that evidence clearly (Clause 7.2). Amgen alleged that promotional material which relied on Goldsmith *et al* and ignored the conclusions of the well designed, prospective, randomised study of Tolman *et al* (2005) did not comply with the Code. Tolman *et al* demonstrated that dose increases were required with NeoRecormon. The conference displays were neither fair nor balanced and were not an up to date evaluation of all the evidence.

Tolman *et al* evaluated the doses of NeoRecormon and Aranesp needed to maintain stable haemoglobin. 162 unselected haemodialysis patients were converted from thrice-weekly SC NeoRecormon to weekly administration of Aranesp (n=81) or NeoRecormon (n=81). After 9 months, the difference in haemoglobin level and dose between the two treatment arms was measured. The study showed that to maintain haemoglobin levels, a significantly higher dose of NeoRecormon than Aranesp was required ($p<0.001$). The mean dose of NeoRecormon was 44% higher than the dose of Aranesp at the end of the study.

These results clearly contradicted Goldsmith *et al*. As a retrospective analysis, Goldsmith *et al* had a lower evidential value than Tolman *et al* and could not be used to disprove the results of Tolman *et al*. As it was, Tolman *et al* was not even mentioned in the conference materials. Furthermore, Roche failed to provide the relevant details of Goldsmith *et al* to enable readers to evaluate it for themselves. Amgen considered that Roche's misleading claims in relation to dose reduction were compounded by their use in a slide presentation of graphs which referred only to Roche data on file and Goldsmith *et al* and not to Tolman *et al*. Copies of selected slides, including the slide containing the graphs, were subsequently circulated by Roche at the congress. Amgen alleged that the exhibition panel, the brochure and the graphs were all in breach of Clause 7.2 of the Code.

RESPONSE

Roche stated that the claim was referenced solely to Goldsmith *et al*. However, Roche disputed that this was not a true representation of the current state of scientific research and of the available data. Data supplied to Amgen confirmed that the majority of multicentre, randomised, peer-reviewed published clinical studies that demonstrated dose difference between patients on darbepoetin and epoetin confirmed that, assuming that dose ratio was 200:1 as per Aranesp summary of product characteristics (SPC), a relatively smaller dose of SC epoetin was required than SC darbepoetin (Locatelli *et al* 2003; Locatelli *et al* 2001; Macdougall *et al* 2003; Vanrenterghem *et al* 2002 and Locatelli *et al* 2002).

The SPC for Aranesp recognised that the doses for IV darbepoetin and SC darbepoetin were equivalent. However, data suggested that there was a dose reduction required when transferring patients from IV erythropoietin stimulating agents (ESAs) to SC epoetin beta. This suggested that there would be

expected to be a dose reduction between SC darbepoetin and SC NeoRecormon. Locatelli *et al* (2003) reported a 9% increase in darbepoetin dose when switching from SC epoetin beta to SC darbepoetin.

Amgen suggested that excluding Tolman *et al* from the data presented at the congress was misleading but, since it was the only paper that indicated that a higher dose of NeoRecormon than darbepoetin was required in order to achieve the same clinical effect, and the design had not been replicated at any other centre to Roche's knowledge, using as it did a complicated and unique computerised algorithm for determining dose rarely used elsewhere. Thus the balance of evidence supported the claim at issue. Additionally there were a number of other anomalies in the design of this study: it did not compare like with like, with darbepoetin being administered via pre-filled syringes, and yet (despite the availability of prefilled syringes of NeoRecormon) multidose vials of NeoRecormon were used, allowing for a greater degree of dosing error in this group. Tolman *et al* was a single centre study without a true control arm. Once patients had been stabilised on NeoRecormon three times weekly, all patients were then randomised to the once weekly regimen, leaving no patients on the three times weekly dose. Further, two thirds of the patients in the epoetin beta arm were male, while the genders were equally split in the darbepoetin arm.

Interestingly, other studies (Locatelli *et al* 2002 and Weiss *et al* 2000) had demonstrated no dose penalties when changing from thrice weekly to once weekly epoetin beta, and yet Tolman *et al* again stood out as not reflecting the balance of evidence, since patients required a significant dose increase. This had been an ongoing source of inter-company dialogue.

Roche also noted that the majority of the results presented in Tolman *et al* and all presented in abstracts and presentations had been from the per protocol analysis, and although the publication referred to a 'modified' intention to treat only population (ITT), an ITT analysis had, to Roche's knowledge, never been presented. It was well accepted that presenting data only on those patients that completed the study and not on the ITT population led to bias in the results. The lead author of this study was, at the time of acceptance for publication, (as he remained) an Amgen employee although he was not recognised as such in the publication.

Roche therefore refuted the assertion that the use of Goldsmith *et al* was not accurate, balanced, fair and unambiguous. It was indeed an up-to-date and a fair reflection of the evidence available and not in breach of Clause 7.2.

PANEL RULING

The Panel noted that the exhibition panel was headed 'NeoRecormon' in logo format, followed by 'Energy to make a difference. NeoRecormon SC is a cost efficient option for treatment of anaemia'. The claim at issue 'In a retrospective study, a 24% dose reduction has been demonstrated with NeoRecormon SC compared with darbepoetin alfa SC', was referenced to the Revised European Best Practice Guidelines 2004 (EBPG) and appeared as a bullet point immediately above a table, referenced to Goldsmith *et al*, which compared the mean weekly IV and SC doses of NeoRecormon and darbepoetin alfa.

The Panel noted that Goldsmith *et al*, a poster presentation, was a retrospective analysis which assessed anaemia management and current treatment practices with erythropoietins in patients on haemodialysis with particular emphasis on the impact that different erythropoietins and their routes of administration had on haemoglobin (Hb) control. Mean Hb levels were similar between the three cohorts: NeoRecormon, darbepoetin alfa and epoetin alfa. Hb control was defined as the proportion of Hb values within the target range of 10-12g/dl. Mean weekly SC doses for darbepoetin alfa and for epoetin beta were 10,210 IU and 7,890 IU respectively. A 24% dose reduction was possible with SC epoetin beta vs SC darbepoetin alfa.

Tolman *et al* was an open label, prospective, randomized, 9 month study which compared the clinical effectiveness of SC weekly NeoRecormon and darbepoetin alfa on conversion from thrice weekly SC NeoRecormon. There was no control group. Patients were managed according to their Hb levels. Over the course of the study maintenance of Hb levels was associated with a need to increase NeoRecormon doses whilst darbepoetin alfa doses fell. The Hb target range was 11-12g/dl. The mean weekly epoetin beta dose at 9 months was 44% higher than the mean darbepoetin alfa dose (133 IU/kg vs 92 IU/kg). The study authors noted that they had failed to observe complete dose and Hb stabilization in both arms until at least week 28 after conversion.

The Panel noted that Roche had referred to a number of other studies which it considered supported its claim eg Locatelli *et al* (2003), Locatelli *et al* (2001) and Vanrenterghem *et al*. Although these studies showed that lower doses of SC epoetin beta were required than SC darbepoetin the differences between the two were less than the 24% reported by Goldsmith *et al* and ranged from 12.3% to 16.4%. Locatelli *et al* (2003) reported that the dose increase seen in patients on darbepoetin appeared to be due to the fact that they had been sub-optimally controlled whilst on SC epoetin. The studies all differed in the Hb targets which they set.

Overall the Panel considered that the data was such that the claim at issue was an oversimplification of the situation and thus did not represent the balance of the evidence. The claim was misleading as alleged. A breach of Clause 7.2 was ruled.

The Panel noted that the slide depicting the bar chart entitled 'Route of Administration Dose Saving with Epoetin ß SC vs IV' was referenced to data on file and made no comparison with darbepoetin alfa. The subsequent bar chart compared the achievement of Hb target range of all ESAs. The Panel did not know how the slide was presented at the symposium. On the evidence before it the Panel did not consider the slide constituted a misleading comparison with darbepoetin alfa and thus on this narrow point considered that it was not misleading as alleged; no

breach of Clause 7.2 was ruled.

The slide was also reproduced in the brochure alongside the abstract entitled 'Hb Control: Current Clinical Practice'. The Panel did not consider that it invited a comparison with darbepoetin alfa as alleged and on this narrow point no breach of Clause 7.2 was ruled.

2 Treatment of target haemogloblin levels

An exhibition panel headed 'NeoRecormon achieves Hb stability in practice' featured the claims 'In a retrospective study (n=1098) NeoRecormon SC controls Hb levels within a 10-12g/dl range in 75% of haemodialysis patients' and 'Significantly more haemodialysis patients treated with NeoRecormon achieve constant Hb control within a 10-12g/dl range compared with darbepoetin alfa' appeared on a Roche exhibition stand referenced to Goldsmith *et al*.

In connection with a Roche sponsored satellite symposium entitled 'Anaemia Management : from Targets to Reality', Roche distributed a brochure which included a bar chart based on Goldsmith *et al*. The bar chart was headed 'Staying Within Hb Target Range. Are all ESAs Equal' which Amgen stated purportedly showed that Aranesp enabled fewer patients to reach the Hb target range of 10-12g/dl than NeoRecormon.

COMPLAINT

Amgen stated that Roche's claims were misleading in their treatment of target haemoglobin levels. Specifically, the target haemoglobin level (10-12g/dl) used in Goldsmith *et al* did not have real clinical relevance and was inconsistent with the European Best Practice Guidelines (EBPG) that were widely applied in clinical practice throughout Europe. The EBPG recommended that, in general, patients with chronic kidney disease should maintain a target haemoglobin concentration > 11g/dl. Erythropoiesis-stimulation agents should be given to all chronic kidney disease patients with haemoglobin levels consistently < 11g/dl where all other causes of anaemia had been excluded.

Roche accepted this since, in the same Roche-sponsored brochure circulated in connection with its satellite symposium, a haemoglobin level ≥ 11g/dl was said to be 'recommended'. Applying the EBPG, it could be seen, even with Goldsmith at al, that more patients achieved the target level with Aranesp than with NeoRecormon: 58% of Aranesp patients reached Hb > 11g/dl, whereas only 46% of NeoRecormon patients achieved Hb target > 11g/dl. Bizarrely, however, the brochure referred to Goldsmith *et al* which was based on a target haemoglobin of 10-12g/dl, purportedly to demonstrate greater efficacy of NeoRecormon in comparison to Aranesp. A copy of an abstract Hb control: Current Clinical Practice from the brochure was provided. Amgen did not consider that it represented a balanced representation of the evidence. Amgen alleged that this piece misled the reader both by distortion and undue emphasis.

The failure to draw readers' attention either in the exhibition panel claims or the Roche brochure to the fact that Goldsmith *et al* was not consistent with the EBPG was a distortion and directly misled the audience by undue emphasis. The material was not sufficiently complete to enable the reader to form their own opinion of the therapeutic value of the medicine. These claims, therefore, breached Clause 7.2 of the Code.

RESPONSE

Roche stated that the current UK Renal Association guidelines referred to the target haemoglobin level of ≥ 10g/dl with anaemia being diagnosed when haemoglobin levels fell below 12g/dl. This led to the target range of 10-12g/dl being included the protocol for Goldsmith *et al*. The updated EBPG had been published since the initiation of Goldsmith *et al*, but the UK Renal Association continued to recommend that individual patients' Hb levels should be maintained about 10g/dl. It would clearly be misleading and distortion to present the data from this study by using a target Hb level not included within the protocol. Notwithstanding that Roche did when appropriate refer to the EBPG.

Goldsmith *et al* was designed to identify haemodialysis patients who maintained stable haemoglobin levels within a target range of 10-12g/dl. Whilst Amgen stated that 58% of darbepoetin alfa patients reached Hb > 11g/dl compared with 46% of NeoRecormon patients, this end point was not included in the study. When presented and understood within the right context, neither the materials nor the symposia speaker distorted or misrepresented the results of Goldsmith *et al*.

Reference was made at the Roche sponsored symposium to the Goldsmith data and the target range that was included in the protocol as discussed above. The data presented in the brochure therefore did not seek to mislead by either distortion or undue emphasis. Further the brochure was only available to those attending the symposium who therefore were subject to the complete oral programme. Amgen had, Roche believed, been somewhat disingenuous by selecting only one page from the brochure provided rather than leaving it in context. Roche firmly considered that the symposium brochure did not breach Clause 7.2 as alleged.

PANEL RULING

The Panel noted that the EBPG Section II 'Targets for anaemia treatment' discussed appropriate haemoglobin targets for anaemia treatment: this was dependent upon patient population and was recommended in general to be > 11g/dl. Goldsmith *et al* stated that Hb control was defined as the proportion of the Hb values within the target range of 10-12g/dl during the 12 month study period. This range reflected current licences and was based on reports relating to clinical outcomes to provide acceptable variability (±1g/dl) around the EBPG Hb target of 11g/dl. The Panel noted Amgen's submission that if the EBPG were applied to the Goldsmith *et al* data more patients achieved the target level with darbepoetin alfa than with NeoRecormon; 58% of darbepoetin alpha patients reached Hb >

11g/dl compared to 46% of NeoRecormon.

The Panel considered that the exhibition panel was not sufficiently complete to enable the reader to form their own opinion of the therapeutic value of the medicine as alleged. The EBPG recommended target was not mentioned. A breach of Clause 7.2 was ruled.

In relation to the brochure the Panel noted that the bar chart at issue depicting data from Goldsmith *et al* accompanied an abstract headed 'Hb Control: Current Clinical Practice'. The abstract began by stating 'International studies and registry data have shown consistent improvement in the management of CKD [chronic kidney disease] related anaemia, with an increasing proportion of patients achieving recommended Hb levels ≥11g/dl with erythropoiesis stimulating agents (ESAs)'.

The accompanying bar chart depicting the results of Goldsmith *et al*, however, referred to an Hb target range of 10-12g/dl and showed that more patients hit this range with NeoRecormon than darbepoetin alpha. The Panel considered that to refer to one target level in the text but to depict results relating to another was inconsistent and thus misleading. A breach of Clause 7.2 was ruled.

3 Claim 'Guidelines favour SC administration for both clinical and economic reasons'

COMPLAINT

Amgen alleged that the statement 'Guidelines favour SC administration for both clinical and economic reasons' was referenced to EBPG was misleading. The EBPG only made such a statement regarding epoetin alfa [sic] (NeoRecormon) and only in CKD patients not undergoing dialysis and in transplant patients. Yet this qualification was not included.

Moreover by placing this statement directly under the comparison with darbepoetin alfa regarding SC dose requirements, this statement amounted to a claim relying on an implicit comparison with Aranesp which was misleading and incapable of substantiation. More specifically under the heading 'Recommendation' the relevant parts of the EBPG stated:

> 'The recommended route of administration is dependent on the patient group being treated and the ESA being used.
>
> - For patients on HD [haemodialysis], the intravenous (i.v.) route may be preferable for comfort and convenience, but the subcutaneous (s.c.) route can substantially reduce the dose requirements of ESA.
> - In CKD patients not undergoing dialysis and in transplant patients, epoetin beta should preferably be given s.c. for both economic and practical reasons.
> - Epoetin alfa (Eprex, Erypo) is not licensed for s.c. administration in all CKD patients in many European countries (including all member states of the European Union) due to the risk of pure red cell aplasia (PRCA).
> - Darbepoetin alfa can be given either i.v. or s.c. without dose adjustments in all CKD patients. In HD patients, darbepoetin alfa may be easier to administer i.v., but the s.c. route is preferable in all other CKD patients.'

Therefore the statement that SC was recommended for economic and practical reasons was only true and capable of substantiation for epoetin alfa and epoetin beta. It was not true or capable of substantiation for darbepoetin alfa. With darbepoetin alfa, the IV route of administration was as cost efficient as SC administration. Accordingly, the EBPG specifically pointed out that darbepoetin alfa, in contrast to NeoRecormon, could be administered either IV or SC without dose adjustments. Again this directly relevant fact was noticeably absent on the exhibition panel.

Amgen alleged a breach of Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

Roche stated that Amgen had mistakenly referred to NeoRecormon as epoetin alfa, but the guidelines did state that in CKD epoetin beta (NeoRecormon) should be administered preferably via the SC route. However the above statement used at the congress referred to the overall position of the EBPG. Guideline III.II referred to the route of administration of epoetin, suggesting that:

- 'For patients on HD the intravenous route (IV) may be preferable for comfort and convenience, but the subcutaneous route (SC) may substantially reduce the dose requirements of ESA' (Evidence level A)
- 'In CKD patients not undergoing dialysis and in transplant patients epoetin beta should preferably be given subcutaneously for both economic and practical reasons'
- 'Patients on dialysis should preferably be given epoetin beta subcutaneously for economic reasons' (Evidence level A)
- 'Epoetin alfa (Eprex, Erypo) is not licensed for SC administration in all CKD patients in many European countries (including all member states of the European Union) due to the risk of pure red cell aplasis (PRCA)' (Evidence level B)
- 'Darbepoetin alfa can be given either IV or SC without dose adjustments in all CKD patients. In HD patients, darbepoetin alfa may be easier to administer but the SC route is preferable in all other CKD patients' (Evidence level B).

Roche therefore believed that the EBPG fully supported its statement that they favoured SC administration for both clinical and economic reasons and Roche completely refuted the suggestion that this statement was in breach of Clauses 7.2, 7.3 and 7.4 of the Code, being neither inaccurate, unbalanced, unfair, unobjective nor ambiguous. It did not mislead and did not seek to compare NeoRecormon with Aranesp.

PANEL RULING

The Panel noted that the claim at issue appeared on the same exhibition panel as the comparative bullet

point at issue at point 1 above and immediately beneath a table comparing the mean weekly SC and IV dose of NeoRecormon and darbepoetin alfa. The exhibition panel also featured some claims which were clearly only about NeoRecormon. Given the context in which it appeared it was unclear as to whether the claim 'Guidelines favour SC administration for both clinical and economic reasons' related only to NeoRecormon or was a comparison of NeoRecormon with darbepoetin alfa.

The Panel noted that the introductory paragraph of Guideline III.II of the EBPG read 'The recommended route of administration is dependent on the patient group being treated and the type of ESA used'. The Panel noted the economic, clinical and practical points listed in relation to the route of administration and choice of epoetin for each patient group. Economic reasons were mentioned in relation to NeoRecormon SC for patients on dialysis, CKD patients not undergoing dialysis and in transplant patients. A table summarizing the recommendations gave SC administration as the recommended route for all patient types.

The guidelines stated that darbepoetin alfa could be given either IV or SC without dose adjustment in all CKD patients. In HD patients, darbepoetin alfa might be easier to administer IV but the SC rate was preferable in all other CKD patients. Given that there was no dose difference between IV and SC darbepoetin there was no economic reason to use the SC route. The Panel considered that given the context in which it appeared, the claim 'Guidelines favour SC administration for both clinical and economic reasons' was misleading about the guidelines' recommendations for darbepoetin alfa and not capable of substantiation in this regard. Breaches of Clauses 7.2, 7.3 and 7.4 were ruled.

Complaint received **27 July 2006**

Case completed **4 December 2006**

CASE AUTH/1871/7/06

DOCTOR v SANOFI-AVENTIS

Acomplia journal advertisement

A doctor complained about an advertisement for Acomplia (rimonabant) issued by Sanofi-Aventis and published in GP. Acomplia was indicated as an adjunct to diet and exercise for the treatment of obese patients ([Body Mass Index] BMI ≥30kg/m^2), or overweight patients (BMI >27kg/m^2) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia.

The complainant alleged that the advertisement was misleading and suggested that Acomplia could be used to treat all cardiometabolic risk factors associated with diseases such as diabetes mellitus and cardiovascular disease.

The suggestion that half of its effects on cardiometabolic risk factors were beyond those expected by weight alone was misleading and suggested that Acomplia had other as yet unproven effects on all cardiometabolic risk factors including those cited in its summary of product characteristics (SPC); this was not consistent with the licensed indication which was in essence to reduce weight in obese or overweight patients. If one of the consequences of this very specific use was an improvement in the overall cardiometabolic risk profile of patients then that was fine.

The advertisement implied that Acomplia had some, as yet unidentified, effect of reducing specific cardiometabolic risk factors and that it should therefore be used to treat overweight/obese patients with high-blood pressure, low HDL-c, high triglycerides, insulin resistance and abnormal inflammatory markers and HbA1c levels. What proof was there to suggest a direct and causal link between the effects of Acomplia on any of the latter parameters other than an indirect effect associated with weight reduction? If Acomplia was so effective in modulating dyslipidaemia it was paradoxical that it had no significant effect on elevated LDL-c and total-c levels, both established cardiometabolic risk factors, a fact glaringly omitted from the advertisement?

Encouraging the unlicensed use of Acomplia was further evidenced by the nonsensical statement that cardiometabolic risk factors in overweight patients could be where you least expected them. The latter clearly suggested that obesity or being overweight should not be considered as a cardiometabolic risk in isolation but should consider the effect of Acomplia on other less obvious risk factors. Thus doctors were invited to pay scant regard to the specific indication in weight reduction with the promise that Acomplia additionally modulated other independent cardiometabolic risk factors independent of weight reduction.

The complainant alleged that the advertisement exaggerated the facts which were that being overweight was a recognized cardiometabolic risk factor in its own right and that Acomplia treated only this particular parameter; any suggestion that the effects of Acomplia in modulating cardiometabolic risk factors went beyond weight reduction was patently misleading.

The Panel noted that the left hand side of the advertisement featured an outline of an overweight patient with the statement 'Cardiometabolic risk factors in overweight patients can be where you least expect them'. The right hand side was headed 'Discover Acomplia' followed by the licensed

indication. This was followed by reference to cardiometabolic risk factors, listing established risk factors as elevated blood glucose, high LDL-c and high blood pressure and emerging risk factors as low HDL-c, abdominal obesity, high triglycerides, insulin resistance and inflammatory markers. These were followed by information about reductions in weight and waist circumference. The final part of this section stated that Acomplia compared to placebo demonstrated significantly greater improvements in glycaemic control, HbA1c, increases in HDL-c and reductions in triglycerides. This was followed by the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone'.

The Panel considered that the overall impression of the advertisement was that Acomplia was to be prescribed in overweight patients because of its effects on all cardiometabolic risk factors, not that Acomplia was to be prescribed for weight management as an adjunct to diet and exercise for the treatment of obese patients and overweight patients with associated risk factors such as type 2 diabetes or dyslipidaemia. In that regard the Panel noted that the statement 'Cardiometabolic risk factors in overweight patients can be where you least expect them' appeared in very much larger type size than any of the information about weight loss. The emphasis of the advertisement was not on the licensed indication in the SPC but on the information on pharmacodynamic properties. This impression was reinforced by the strapline, 'It's not what you lose. It's what you gain'. In that regard the Panel considered that the success or otherwise of Acomplia therapy should be measured by weight loss not by alterations in cardiometabolic risk factors.

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

The licensed indication was included in the advertisement but was not the most prominent message. The Panel did not accept Sanofi-Aventis' view that the weight loss indication was clearly presented and given priority over the additional effects of Acomplia. It agreed with Sanofi-Aventis that weight loss was relatively more important in the SPC than the additional effects.

The Panel considered that the advertisement had not placed the cardiometabolic risk factors sufficiently within the context of the licensed indication. In the Panel's view the most prominent message was that Acomplia was to be prescribed for its effects on cardiometabolic risk factors in overweight patients and this was inconsistent with the SPC. A breach of the Code was ruled. This ruling was upheld on appeal by Sanofi-Aventis.

The Panel accepted that approximately 50% of the mean improvements in glycaemic control (HbA1c), HDL-c and triglycerides in patients receiving Acomplia were beyond that expected from weight loss alone. This was clearly stated in the SPC. Thus effects on some cardiometabolic risk factors beyond those expected from weight loss alone had been established. The advertisement, however, stated that 'Cardiometabolic Risk Factors include established and emerging factors…'. The Panel thus did not accept the submission that the claim 'An established 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' applied to three risk factors, HbA1c, HDL-c and triglycerides; it appeared to apply to them all. The claim was misleading in this regard and thus not capable of substantiation. Breaches of the Code were ruled. These rulings were upheld on appeal by Sanofi-Aventis.

The Panel did not consider that the circumstances justified a ruling that high standards had not been maintained. Nor did the Panel consider that the circumstances justified a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure. These rulings were upheld on appeal by the complainant.

A doctor complained about an advertisement for Acomplia (rimonabant) (ref RIM06/335) issued by Sanofi-Aventis that appeared in GP. According to Section 4.1 of the summary of product characteristics (SPC) Acomplia was indicated as an adjunct to diet and exercise for the treatment of obese patients ([Body Mass Index] BMI ≥30kg/m^2), or overweight patients (BMI >27kg/m^2) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia. Section 4.1 referred readers to Section 5.1, pharmacodynamic properties, which included details of clinical study results.

COMPLAINT

The complainant alleged that the advertisement was misleading and suggested that Acomplia could be used to treat all cardiometabolic risk factors associated with diseases such as diabetes mellitus and cardiovascular disease.

The complainant alleged that the suggestion that half of the effects of this medicine on cardiometabolic risk factors were beyond those expected by weight alone was misleading and suggested that Acomplia had other as yet unproven effects on all cardiometabolic risk factors including those cited in its SPC; this was not consistent with the licensed indication which was in essence to reduce weight in obese or overweight patients. If one of the consequences of this very specific use was an improvement in the overall cardiometabolic risk profile of patients then that was fine.

The complainant alleged however, that this advertisement did not articulate the latter reasonable position. In fact it clearly implied that Acomplia had some magical, as yet unidentified, effect of reducing specific cardiometabolic risk factors and that it should therefore be used to treat overweight/obese patients with high-blood pressure, low HDL-c, high triglycerides, insulin resistance and abnormal inflammatory markers and HbA1c levels. What proof was there to suggest a direct and causal link between the effects of Acomplia on any of the latter parameters other than an indirect effect associated with weight reduction? Indeed, if Acomplia was so effective in modulating dyslipidaemia was it not somewhat paradoxical that it had no significant effect on

elevated LDL-c and total-c levels, both established cardiometabolic risk factors, a fact that was glaringly omitted in the advertisement?

The complainant alleged that encouraging the unlicensed use of Acomplia was further evidenced by the nonsensical statement that cardiometabolic risk factors in overweight patients could be where you least expected them. The latter clearly suggested that obesity or being overweight should not be considered as a cardiometabolic risk in isolation but should consider the effect of Acomplia on other less obvious risk factors. Thus doctors were invited to pay scant regard to the very specific indication in weight reduction with the promise that Acomplia additionally modulated other independent cardiometabolic risk factors independent of weight reduction.

The complainant alleged that surely, the requirement to take Acomplia as an adjunct to strict dietary controls and vigorous physical exercise might also have had a direct and significant effect on the improvement of many of the cardiometabolic risk factors mentioned or was it to be assumed, as the advertisement implied, that the impact of positive lifestyle improvements such as smoking cessation, daily exercise and a balanced calorie controlled diet had minimal impact in patients with diabetes or dyslipidaemia when compared with the impact of this medicine? Also what of the additive effect of the primary treatments for diabetes and dyslipidaemia such as statins, insulin, oral hypoglycaemic agents, aspirin etc, which had direct and significant positive effects on cardiometabolic risk factors that were mentioned in the advertisement or was it to be assumed that these had less of an effect compared to Acomplia.

The complainant alleged that the advertisement exaggerated the facts which were that being overweight was a recognized cardiometabolic risk factor in its own right and that Acomplia treated only this particular parameter; any suggestion that the effects of Acomplia in modulating cardiometabolic risk factors went beyond weight reduction was patently misleading.

When writing to Sanofi-Aventis the Authority asked it to respond in relation to the requirements of Clauses 2, 3.2, 7.2, 7.4 and 9.1 of the Code.

RESPONSE

Sanofi-Aventis submitted that this was the first therapeutic agent in a new class; hence it was reasonable to include some background information in the advertising in order to place this therapy in context.

The licensed indication for Acomplia as stated in the SPC was: 'As an adjunct to diet and exercise for the treatment of obese (BMI ≥30kg/m^2) or overweight (BMI >27kg/m^2) patients with associated risk factor(s), such as type 2 diabetes or dyslipidaemia (see section 5.1)'.

This clearly set out the purpose of the medicine as a treatment for obese patients or for overweight patients with additional risk factors, and incorporated into the indication a reference to the additional information on other effects of the medicine which were set out in Section 5.1 of the SPC.

The licensed indication was clearly and prominently placed at the top of the advertisement, which stated that: 'Acomplia is the first selective CB_1 blocker and is indicated for use as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥30kg/m^2), or overweight patients (BMI >27kg/m^2) with associated risk factors such as type 2 diabetes or dyslipidaemia'.

Sanofi-Aventis submitted that the advertisement went on to explain that cardiometabolic risk factors included both established and emerging risk factors, which contributed to the development of type 2 diabetes and cardiovascular disease (Alberti *et al* 2005). It then listed established risk factors: elevated blood glucose, high LDL-c and high blood pressure and emerging risk factors: low HDL-c, abdominal obesity, high triglycerides, insulin resistance and inflammatory markers. No claim was made for the effect of Acomplia on these risk factors, which were referred to for explanatory purposes.

Only then did the text turn to the effects of Acomplia. Weight reduction was the first and primary area covered; there was a clear description that Acomplia demonstrated significantly greater reductions in weight and waist circumference compared with placebo (Data on file, Despres *et al* 2005). This was in accordance with the product's licensed indication.

In addition the advertisement subsequently described other observed effects of Acomplia, namely that, in comparison to placebo it demonstrated significantly greater improvements in glycaemic control (HbA1c), increases in HDL-c and reductions in triglyerides (Data on file, Despres *et al*).

Finally the advertisement stated that: 'An estimated 50% of the effects of Acomplia on cardiometabolic risk factors are beyond those expected from weight loss alone'. This statement immediately followed the bullet points relating to particular individual risk factors and hence referred specifically to them.

With regard to the allegation that Acomplia was being promoted outside of its licence including claims for effects on all cardiometabolic risk factors which were misleading and unsubstantiable, Sanofi-Aventis submitted that the licensed indication and its expression in the advertisement were discussed in detail above. The weight loss indication was clearly presented and given priority in the advertisement over the additional effects of Acomplia. This was consistent with their relative importance in the SPC.

Regarding the assertion that claims were made for all cardiometabolic risk factors, the advertisement was worded carefully to make claims only for those risk factors which were within the licence for Acomplia and for which data were available to substantiate the statements made. As stated previously, background information on the rationale for this new class of therapeutic agent was included for clarity.

With regard to the allegation that the advertisement did not emphasise the indication, ie weight loss, and did not emphasise the importance of diet and exercise in this patient population, Sanofi-Aventis submitted that the advertisement clearly described the use of Acomplia as an adjunct to diet and exercise at the outset, as stated above and did not diminish the importance of lifestyle

modification, whilst presenting the beneficial effects of the product. The intrinsic requirement for a diet and exercise regime in patients taking Acomplia was reiterated in the prescribing information. Additionally, whilst the importance of lifestyle modification was recognised, the Phase III studies included diet and exercise in both placebo and active arms, and clearly demonstrated benefit of Acomplia over and above such lifestyle modification alone.

With regard to the allegation that the picture was misleading as it did not emphasise the importance of obesity but directed attention to other risk factors, Sanofi-Aventis submitted that with regard to the figure represented in the advertisement, this highlighted the possibility that cardiometabolic risk factors in overweight patients could be where they were least expected, ie related to obesity and overweight. It did not claim or imply that established risk factors were not important, but aimed to raise awareness of the importance of obesity and overweight as being significant risk factors. This was supported by evidence from the highly regarded INTERHEART study which demonstrated that the population attributable risk for acute myocardial infarction was around 20% for abdominal obesity (Yusuf *et al* 2004) and that this was a greater level of risk than that of diabetes or hypertension for this outcome.

With regard to the allegation that the claims for Acomplia's effect beyond weight reduction were incorrect and misleading, Sanofi-Aventis submitted that the claims relating to the effect beyond weight loss were based on the outcome of the pre-specified analysis of covariance (ANCOVA) of changes in HbA1c, HDL-c and triglycerides with respect to weight loss, carried out and published in the rimonabant in obesity trials (Data on file, Despres *et al*). This analysis and these trials provided the evidence by which the statement regarding the effects beyond weight loss was validated and incorporated into the SPC. Thus the complainant's view that 'any suggestion that the effects of Acomplia in modulating cardiometabolic risk factors went beyond weight reduction was patently misleading' was incorrect.

Sanofi-Aventis submitted that although the mechanism of this effect beyond weight loss was not as yet clearly understood, pre-clinical data had provided some insight as to possible mechanisms of action. Cannabinoid CB_1 receptors had been found to have an effect in adipocytes (Bensaid *et al* 2003), hepatocytes (Osei-Hyiaman *et al* 2005), the gastrointestinal tract (Gomez *et al* 2002) and skeletal muscles (Liu *et al* 2005). The action of CB_1 receptors in these sites had been shown to effect the levels of adiponectin in adipocytes (Bensaid *et al* 2003), the expression of SREBP-1c in hepatocytes (Osei-Hyiaman *et al* 2005), to be involved in the actions of signalling systems that promote the perception of satiety in the gastrointestinal tract (Gomez *et al* 2002), and to have a role in glucose uptake in skeletal muscle (Liu *et al* 2005). However, it was important that the strength of the clinical evidence which had led to the licence indication and wording in the SPC was not confused with the evolving understanding of mechanisms of action, for a compound which was, after all, first in its class.

Sanofi-Aventis noted the complainant's allegation that the advertisement failed to recognise the beneficial effect of other licensed medicines treating various cardiometabolic risk factors. Sanofi-Aventis submitted that it was not the remit or a requirement of the advertisement to describe the beneficial effects of other products currently licensed for treatment of individual cardiometabolic risk factors. If the complainant had referred to the effect of concomitant medications in patients enrolled in the rimonabant studies, these were randomised placebo-controlled, double-blind studies designed to eliminate such bias.

Sanofi-Aventis submitted that the advertisement did not promote Acomplia in a manner inconsistent with its product license; in particular, no claims were made for the effects of Acomplia on parameters which were not referred to in the SPC and substantiated by independent research (Clause 3.2). The information, claims and comparisons accurately reflected the licence and supporting published data and were balanced in terms of appropriate reference to diet and exercise requirements (Clause 7.2); equally, they were substantiated by independent research published in peer-reviewed journals (Clause 7.4). High standards had therefore been maintained (Clause 9.1).

In conclusion, Sanofi-Aventis submitted that the advertisement clearly and responsibly described the licensed indication for Acomplia, did not mislead, misrepresent or make inappropriate claims regarding the product and satisfied the requirements of Clauses 2, 3.2, 7.2, 7.4 and 9.1 of the Code.

PANEL RULING

The Panel noted that the left hand side of the advertisement provided by Sanofi-Aventis featured an outline of an overweight patient with the statement 'Cardiometabolic risk factors in overweight patients can be where you least expect them'. The right hand side was headed 'Discover Acomplia' followed by the licensed indication. This was followed by reference to cardiometabolic risk factors listing established risk factors as elevated blood glucose, high LDL-c and high blood pressure and emerging risk factors as low HDL-c, abdominal obesity, high triglycerides, insulin resistance and inflammatory markers. These were followed by information about reductions in weight and waist circumference. The final part of this section stated that Acomplia compared to placebo demonstrated significantly greater improvements in glycaemic control, HbA1c, increases in HDL-c and reductions in triglycerides. This was followed by the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone'.

The Panel considered that the overall impression of the advertisement was that Acomplia was to be prescribed in overweight patients because of its effects on all cardiometabolic risk factors not that Acomplia was to be prescribed for weight management as an adjunct to diet and exercise for the treatment of obese patients and overweight patients with associated risk factors such as type 2 diabetes or dyslipidaemia. In that regard the Panel noted that the statement 'Cardiometabolic risk factors in overweight patients

can be where you least expect them' appeared in very much larger type size than any of the information about weight loss. The emphasis of the advertisement was not on the licensed indication as set out in Section 4.1 of the SPC but on the information in Section 5.1, pharmacodynamic properties. This impression was reinforced by the strapline, 'It's not what you lose. It's what you gain'. In that regard the Panel considered that the success or otherwise of Acomplia therapy should be measured by weight loss not by alterations in cardiometabolic risk factors.

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

The Panel noted that the licensed indication was included in the advertisement but was not the most prominent message. The Panel did not accept Sanofi-Aventis' view that the weight loss indication was clearly presented and given priority over the additional effects of Acomplia. It agreed with Sanofi-Aventis that the weight loss was relatively more important in the SPC than the additional effects.

The Panel considered that the advertisement had not placed the cardiometabolic risk factors sufficiently within the context of the licensed indication. In the Panel's view the most prominent message was that Acomplia was to be prescribed for its effects on cardiometabolic risk factors in overweight patients and this was inconsistent with the SPC. A breach of Clause 3.2 of the Code was ruled.

The Panel was unsure what was meant by the claim that cardiometabolic risk factors 'can be where you least expect them' and Sanofi-Aventis' submission that the aim was to raise awareness of the importance of obesity and being overweight as significant risk factors. In the Panel's view the intended audience would be well aware that obesity and overweight were significant risk factors. It might be that the audience would not appreciate that established risk factors in diabetes or hypertension might be less than the obesity risk factors and in this regard Sanofi-Aventis provided data in relation to the risk of acute myocardial infarction in abdominal obesity. The Panel was unsure that this message would be apparent from the claim.

The Panel accepted that approximately 50% of the mean improvements in glycaemic control (HbA1c), HDL-c and triglycerides in patients receiving Acomplia were beyond that expected from weight loss alone. This was clearly stated in Section 5.1 of the SPC. Thus effects on some cardiometabolic risk factors beyond those expected from weight loss alone had been established. The advertisement, however, stated that 'Cardiometabolic Risk Factors include established and emerging factors…'. The Panel thus did not accept the submission that the claim 'An established 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' applied to three risk factors, HbA1c, HDL-c and triglycerides; it appeared to apply to them all. The claim was misleading in this regard and thus not capable of substantiation.

Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel did not consider that the circumstances justified a ruling of a breach of Clause 9.1 and ruled accordingly. Nor did the Panel consider that the circumstances justified a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.

APPEAL BY SANOFI-AVENTIS

Sanofi-Aventis appealed the Panel's rulings of breaches of Clauses 3.2, 7.2 and 7.4. In summary, Sanofi-Aventis submitted that:

- Obesity was a serious medical condition that caused health problems such as diabetes and heart disease. Treatment aimed to reduce morbidity and mortality through reducing weight and improving risk factors.
- The advertisement was intended to convey an important educational message regarding the modern understanding of obesity and its management, in addition to introducing Acomplia.
- The Panel's ruling was based on an understanding that Acomplia was indicated for weight management. However, the actual indication was for the treatment of obese patients or overweight patients with associated risk factors, in keeping with the modern understanding of obesity as a disease.

Sanofi-Aventis explained that the understanding of obesity as a disease had advanced considerably in the last decade. Even small degrees of weight loss in patients with an increased risk of cardiovascular disease led to a significant reduction in the risk to health, through improvement in multiple cardiometabolic risk factors and a demonstrable reduction in the incidence of cardiovascular events (Eilat-Adar *et al* 2005). The definition of treatment success was now accepted as modest weight loss (as little as 5% of body weight in a moderately overweight patient) accompanied by improvements in risk factors for cardiovascular and metabolic disease.

Sanofi-Aventis submitted that fat tissue was not an inert storage organ but was highly dynamic, involved in a diverse range of physiological and metabolic processes, and responsible for the production of over fifty adipokines – proteins with signalling properties and functional roles that included energy balance, insulin sensitivity and lipid metabolism (Ronti *et al* 2006). Therefore many adverse effects were amplified when fat tissue was present in excess. Finally, there was a clear understanding of the long-recognised observation that the location of fat tissue was important in respect to adverse effects – fat tissue in the abdomen was more active metabolically than subcutaneous fat and was particularly linked to ill health (Després *et al* 2001).

Sanofi-Aventis submitted that these recent advances in medical science underpinned the current rationale for treating obesity as a disease. As obesity pre-disposed to both metabolic and cardiovascular comorbidities (such as type 2 diabetes and cardiovascular disease), the aim of treatment was to achieve realistic gradual weight loss and prevent the morbidity and mortality associated with obesity,

without undue adverse effects. (Atterburn and Noel 2004). Patients in whom treatment was particularly indicated were those with comorbidities such as coronary heart disease and diabetes.

Sanofi-Aventis submitted that the advertisement was intended to ensure that Acomplia was used responsibly by health professionals, reinforcing the concept that in patients who were overweight or obese, intervention was best reserved for those whose condition was complicated by comorbidities. A significant component of the advertisement was devoted to informing readers about the association between obesity and cardiometabolic risk factors, the understanding of which was central to the modern paradigm of disease management. The intent of the red man graphic and statements on cardiometabolic risk factors being where you least expect them were to raise awareness that obesity was not a cosmetic condition, but could be a serious medical condition implicated in the development of risk factors for cardiovascular and metabolic disease.

Sanofi-Aventis noted Acomplia was indicated (Section 4.1 of the SPC) 'As an adjunct to diet and exercise for the treatment of obese patients (BMI ≥30kg/m^2), or overweight patients (BMI >27kg/m^2) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia (see Section 5.1)'. There was no mention of weight or weight management in this indication. Effects on weight were instead presented alongside those on other cardiometabolic risk factors (specifically those listed in the advertisement HDL-c, triglycerides and glycaemic control as assessed by HbA1c). This was in contrast to earlier treatments for obesity – for example, Reductil (sibutramine), another agent for the treatment of obesity which was licensed five years before Acomplia, had an indication that specifically referred to weight management (Reductil SPC).

Sanofi-Aventis submitted that this background underpinned the basis on which it was appealing the Panel's rulings. To summarise the points under consideration, the complainant made allegations that included the following:

- The advertisement suggested that weight should not be considered in isolation and that other risk factors should be considered important in obese/overweight patients, which were not in keeping with the 'very specific indication for Acomplia' of 'weight reduction'.
- There was no evidence to support the claim that Acomplia had any effects beyond weight loss.

Sanofi-Aventis noted that with respect to these allegations, the Panel had made the following observations:

Firstly, the Panel had decided that taken as a whole, the advertisement had not given the impression that Acomplia was to be prescribed for an indication of weight management, noting that the advertisement did not appear to be in support of the licensed indication set out in Section 4.1 of the SPC, but based around information on other benefits provided in Section 5.1. A breach of Clause 3.2 had been ruled.

Sanofi-Aventis appealed the ruling on the basis that weight management *per se* was not the licensed indication for Acomplia. The SPC clearly stated in Section 4.1 that Acomplia was indicated for the treatment of obese and overweight patients; there was no mention of weight or weight management in this indication (Acomplia SPC). Whilst not specifically referred to in the indication (Section 4.1), the efficacy of Acomplia in both weight management and on cardiometabolic risk factors were all contained in Section 5.1 of the SPC, to which Section 4.1 referred. These effects were all described within the advertisement, and presented in the order in which they were listed in the SPC (this interpretation of the licence was developed and agreed during discussion with the Medicines and Healthcare products Regulatory Agency prior to launch).

Sanofi-Aventis submitted that the aim of medical management of these conditions was to reduce the burden of metabolic or cardiovascular disease, not simply to reduce weight. Sanofi-Aventis understood that the Panel had perceived weight management to be the indication (Section 4.1of the SPC), and had made its rulings based on this. Sanofi-Aventis considered that expressing all the benefits of the product was in keeping with the requirements of the Code, and that through its ruling the Panel was giving direction to limit promotion to only a portion of the information within Section 5.1 (weight management), rather than allowing all of the detail within Section 5.1 of the SPC to be presented.

Secondly, the Panel had decided that the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' appeared to apply to more than the risk factors listed in the advertisement and was therefore misleading in breach of Clauses 7.2 and 7.4. The Panel had accepted that with respect to improvements in the risk factors listed, this claim was accurate and clearly presented in the SPC.

Sanofi-Aventis appealed this ruling on the basis that the statement 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' was not a claim that Acomplia reduced risk factors. It was simply a qualifying statement that outlined how much of an effect was due to weight loss in those risk factors on which Acomplia had an effect. As this was a qualifying statement, it could only make sense if the benefits of Acomplia on risk factors were known, and these were clearly presented adjacent to this additional piece of information.

Sanofi-Aventis submitted in conclusion that this advertisement had been produced with the aim of informing readers about the links between obesity and serious medical conditions and to encourage responsible prescribing (ie restricted to a cohort of patients who were obese or overweight but with associated risk factors). Preliminary results from a drug utilisation study suggested that this approach resulted in rational use of Acomplia in the UK, with use in a BMI < 30kg/m^2 in the absence of a comorbid condition being found in only 3 out of 338 patient records that had been studied. Overall, a high proportion of all patients studied had been found to have one or more additional risk factors for cardiovascular or metabolic disease.

COMMENTS FROM THE COMPLAINANT

The complainant stated that it was patronising to suggest that most physicians were not cognisant of the modern understanding of obesity and its management. It was widely recognised that it was primarily the clinical effect of weight reduction that led to improving cardiometabolic risk factors. This was not what the advertisement conveyed for all of the reasons previously outlined. If the purpose was not to promote off-licence and extrapolate to include unlicensed effects, then might one ask why in the advertisement reductions in weight and waist circumference, cardiometabolic risk factors appropriately associated with the licensed clinical effect of Acomplia ie weight loss, appeared in a conspicuous red typeset and directly associated with improvements in glycaemic control, increases in HDL-c and reductions in triglycerides which were also in red type? Was this not an example of marketing aimed at the unsuspecting reader?

The complainant alleged that the assertion that the product indication made no mention of weight or weight management was patently absurd given that it did mention the terms 'obese patients, BMI >27kg/m^2 and overweight patients'. Could Sanofi-Aventis advise physicians in need of education precisely how they were to identify obese and overweight patients for treatment with Acomplia and in keeping with the wording of the SPC if not by first measuring their weight and then identifying any other associated risk factor(s)?

Indeed if one was to refer to the specific wording in the SPC then what did Sanofi-Aventis have to say with regards to the fact that the SPC clearly indicated that the only effect relevant to prescribers with respect to Acomplia's licensed indication was in fact 'weight loss' by use of the wording 'The clinical effect (weight loss) of rimonabant…'.

The complainant considered that Sanofi-Aventis' appeal was a cynical attempt to prolong the use of the advertisement.

APPEAL BOARD RULING

The Appeal Board agreed with the Panel's view that the emphasis in the advertisement was on cardiometabolic risk factors. In addition the Appeal Board noted that the generally accepted definition of 'overweight' was BMI >25kg/m^2. Although the Acomplia SPC stated it was indicated for use in overweight patients such patients had to have a BMI >27kg/m^2 and associated risk factors such as type 2 diabetes or dyslipidaemia. This was not sufficiently clear in the advertisement. The prominent statement on the left hand part of the advertisement 'Cardiometabolic risk factors in overweight patients' implied that Acomplia could be used in all overweight patients with cardiometabolic risk factors which was not so. There were a group of patients (BMI >25kg/m^2 <27kg/m^2) for whom Acomplia was not indicated. The detail was given in smaller print on the right hand part of the advertisement.

The Appeal Board considered that the inclusion in the advertisement of an outline of an overweight patient with the statement that cardiometabolic risk factors were 'where you least expect them' over their waist, drew attention to abdominal obesity. The Appeal Board noted Sanofi-Aventis' submission regarding the differences between abdominal fat and subcutaneous fat and that abdominal obesity was a cardiovascular risk factor in its own right. The Appeal Board noted that it was possible for a person to be abdominally obese but to still have a BMI <27kg/m^2. Acomplia was to be prescribed according to a patient's BMI and, if this was above 27kg/m^2 and below 30kg/m^2, then the patient needed to have associated risk factors such as type 2 diabetes or dyslipidaemia; abdominal obesity *per se* was not the reason to prescribe.

Overall, the Appeal Board considered that the advertisement had not placed the cardiometabolic risk factors sufficiently in the context of the licensed indication. Thus the Appeal Board upheld the Panel's ruling of a breach of Clause 3.2. The appeal on this point was unsuccessful.

The Appeal Board accepted that approximately 50% of the beneficial effects in glycaemic control (HbA1c), HDL-c and triglycerides in patients receiving Acomplia were beyond that expected from weight loss alone. This was clearly stated in Section 5.1 of the SPC. Thus effects on some cardiometabolic risk factors beyond those expected from weight loss alone had been established. The advertisement mixed information about cardiometabolic risk factors with promotional messages about Acomplia. Readers were told that 'Cardiometabolic Risk Factors include established and emerging factors …' and then given a list of such risk factors. At the end of that particular section of text, and in the same type size and font 'Cardiovascular Risk Factors' were again referred to. The Appeal Board considered that readers would thus assume that the statement 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' encompassed all of the foregoing cardiometabolic risk factors and not the final three as submitted by Sanofi-Aventis. The claim was misleading in this regard and thus not capable of substantiation. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal on this point was unsuccessful.

APPEAL BY THE COMPLAINANT

The complainant appealed the Panel's rulings of no breach of Clauses 2 and 9.1.

The complainant was encouraged by the findings but surprised that these misleading advertisements continued to appear in a myriad of journals. Surely, given the Panel's rulings, these needed to be promptly withdrawn? The complainant was particularly concerned about this because he was now also aware that this misleading information was not restricted to the advertisements but was also being peddled by certain Sanofi-Aventis sponsored physicians. There was no doubt that this misleading information was being used by the company representatives and that all of these activities had occurred in the full knowledge of the company's senior management. The complainant urged the Appeal Board to look into the whole programme of how Sanofi-Aventis

promoted Acomplia beyond the advertisements.

The complainant alleged that the continued dissemination of this misleading information, which was inconsistent with the licensed indication of Acomplia, was testament to the fact that Sanofi-Aventis had and continued to bring the pharmaceutical industry into disrepute. If ever a sign of particular censure was mandated then surely this was an example of where it should be applied. The complainant understood that, the Panel had previously made very similar and clear rulings about the promotion of other newly launched anti-obesity drugs. Did it not occur to Sanofi-Aventis to learn from these past precedents? Clearly not; which was why it had also failed to take the necessary steps to maintain high standards.

The complainant was unconvinced that the Appeal Board had any real power to bring such negligent activity to book but it at least provided a minimum avenue for concerns to be aired. Finally, the complainant stated that he was not motivated by a pathological dislike of the industry; in fact he was positively predisposed towards the important role it had to play in the delivery of real health improvements. However, until the sort of activity undertaken by Sanofi-Aventis was addressed seriously then there would always be a climate of scepticism towards the pharmaceutical industry.

COMMENTS FROM SANOFI-AVENTIS

Sanofi-Aventis noted that the complainant's appeal appeared to make the following points:

- This advertisement, and associated items within the promotional campaign, were still in use despite the initial ruling of the Panel.
- This activity brought the industry into disrepute, as Sanofi-Aventis was not maintaining high standards (Clause 9.1), and deserved particular censure (Clause 2).

Sanofi-Aventis submitted that its response could only be made with reference to the original complaint. In its ruling, the Panel considered that there was widespread understanding of obesity as a risk factor for cardiovascular and metabolic disease. Sanofi-Aventis submitted that emerging risk factors were not widely appreciated – a 2006 survey showed that only around a third of doctors recognised abdominal obesity and a quarter recognised HDL-c /triglycerides as risk factors in their own right. Providing education around these risk factors was therefore meeting a true need with respect to education. Education such as this was a positive component of promotional material, and rather than being a sign of poor standards and deserving particular censure, this was an activity that actually highlighted a positive contribution to improving health, one of the industry's primary objectives. On this basis, the company strongly disagreed with the complainant's suggestion that high standards had not been maintained and that this activity was a discredit to the industry.

Sanofi-Aventis noted the complainant's suggestion that it had not learnt from previous companies' activities in this therapeutic area. Whilst recognising that a previous ruling could only be judged on its own merits, the most relevant case appeared to be concerned with the promotion of use in groups of patients with risk factors that were specifically contraindicated (Case AUTH/1197/6/01). The company agreed with the interpretation of the Panel at the time that this was inappropriate, on the basis that this compromised patient safety by encouraging inappropriate prescribing. However, this was not relevant to the Acomplia advertisement as it did not suggest that the product be used in any contraindicated condition, and neither had this been suggested by either the complainant or Panel.

In summary, Sanofi-Aventis agreed with the Panel's original decision that high standards had been maintained throughout and that there was no activity warranting particular censure.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant countered the fallacious argument that an advertisement was an appropriate and responsible platform from which to 'provide education' on a topic which often filled entire chapters and textbooks. Had this advertisement been an advertorial one might have conceded this suggestion but how did an A3 sized advertisement comprising in the main a red silhouette of an obese individual constitute education?

APPEAL BOARD RULING

The Appeal Board, although noting its ruling above, did not consider that the circumstances justified a ruling of a breach of Clause 9.1 of the Code and it thus upheld the Panel's ruling of no breach. Nor did the Appeal Board consider that the circumstances justified a ruling of a breach of Clause 2 which was reserved as a sign of particular censure. The Appeal Board upheld the Panel's ruling of no breach of Clause 2. The appeal on this point was unsuccessful.

Complaint received **27 July 2006**

Case completed **7 November 2006**

CASE AUTH/1876/8/06

ANONYMOUS EMPLOYEE v PFIZER

Hospital call rates

A Pfizer representative complained anonymously that he/she had been asked to call on target doctors eight times each per year. The complainant knew that this was not in line with the Code and yet if he/she did not carry out these calls he/she risked their job. All hospital representatives were given this call rate and had questioned it many times but nothing had changed.

The Panel noted that the supplementary information to the Code stated, *inter alia*, that the number of calls made on a doctor or other prescriber by a representative each year should not normally exceed three on average. This did not include attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction, all of which could be additional to the three visits allowed. The Code referred to representatives ensuring that the frequency, timing and duration of calls and the manner in which they were made did not cause inconvenience.

According to the documentation representatives were expected to see senior targets 6.5 times in face-to-face meetings during the period December 2005-November 2006. With regard to coverage and frequency, representatives had to 'maintain a robust list of … target doctors and maintain a call rate of 8'.

The Business Planning Guidance 2006 Anti-Infectives identified various customer groups and stated that the coverage was 90% and the frequency 8. A footnote stated that the frequency was to be planned by the representative and agreed with the manager. Not all the customer groups listed were prescribers.

The Panel noted Pfizer's submission that 'call rate' meant 'contact rate'. This was not clear from the enclosures provided by Pfizer. This wording would be altered. In the Panel's view call rate meant a proactive call from a representative on a health professional and would not be interpreted to mean a call responding to a request or an encounter at a meeting or in a corridor.

The documents neither gave any details about the requirements of the Code nor referred the reader to the Code. However, regardless of any reference to the Code and its requirements, the Panel considered that in setting the activity targets so high in relation to call rates, the documents advocated a course of action which would be likely to lead to a breach of the Code. This would be a consequence of following the documentation. Thus the Panel ruled a breach. The Panel did not consider that the circumstances amounted to a failure to maintain high standards and ruled accordingly. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure.

A representative for Pfizer Limited complained anonymously about hospital call rates.

COMPLAINT

The complainant alleged that he/she was asked by the company to call on target doctors eight times each per year. The complainant knew that this was not in line with the Code and yet if he/she did not carry out these calls he/she risked their job. All hospital representatives were given this call rate and had questioned it many times but nothing had changed.

When writing to Pfizer the Authority asked it to respond in relation to Clauses 2, 9.1 and 15.4 of the Code.

RESPONSE

Pfizer noted that Clause 15.4 was intended to protect health professionals etc from being inconvenienced by sales representatives. Pfizer did not believe that the objectives which it set its hospital sales representatives (HSRs) caused health professionals inconvenience.

Pfizer was not aware of having ever received a complaint from a health professional about the frequency of contacts made by HSRs.

Pfizer submitted that all of its representatives (including HSRs) were well trained in the Code and knew that they must comply with it. They were also absolutely clear about the consequences of a complaint. If a health professional were to complain that an HSR's contacts were too frequent, this matter would be urgently discussed between the HSR and their manager and the contact rate amended accordingly. The wishes of individuals on whom HSRs wished to call would therefore be observed.

Pfizer submitted that HSRs were not required to hold 8 formal one-to-one meetings. The reference to 'call rate' in the complaint (and in Pfizer's materials) might be misinterpreted. 'Call rate' in practice actually meant contact rate. Thus Pfizer referred to 'contact(s)' instead of 'call rate(s)' in its submission to aid interpretation. The company would change the terminology it used in its materials in order to avoid misinterpretation in the future.

Although Pfizer required some of its HSRs to make 8 contacts each year with health professionals this did not mean that they had to make 8 formal one-to-one contacts each year. (A formal one-to-one contact was a detailed discussion, usually resulting from an agreed appointment and lasting more than a few minutes). Indeed, Pfizer concurred that to require an HSR to make 8 formal one-to-one contacts might well cause a health professional inconvenience.

Pfizer interpreted the term 'contact' very broadly and

almost any form of meaningful professional contact would count towards an HSR's objectives. It was usually the case that of the 8 contacts required each year, only a small proportion would be in the form of a formal one-to-one meeting; the remainder were usually less formal. For instance, if a health professional was at a departmental meeting at which an HSR was present, that would count as one contact, as would also be the case if both were present at a postgraduate or society meeting etc.

Pfizer submitted that, more often than not, a good proportion of an HSR's contacts would be reactive, as opposed to proactive, because of the close relationship which was built up over time between HSRs and health professionals. Reactive contacts also counted towards an HSR's objectives. Such contacts might include a brief follow-up on a previous meeting in order to deliver a clinical paper, or other information that the health professional had requested, or a relatively brief exchange in a corridor if the HSR and health professional passed each other and had any relevant discussion. Therefore, because of the broad interpretation of what counted as a contact, Pfizer did not think that any inconvenience was caused to health professionals and for that reason there was no breach of Clause 15.4.

Pfizer acknowledged that the supplementary information to Clause 15.4 stated that 'The number of calls made on a doctor or other prescriber by a representative each year should not *normally* exceed three *on average*' (emphasis added). However, for the reasons set out above (namely that of 'contact' was interpreted broadly and consisted of both proactive and reactive contacts in a whole host of settings), Pfizer did not believe that an HSR's objectives contravened the spirit of the Code. The key point in this clause was that inconvenience was not caused to the health professional. There was no evidence of any inconvenience being caused to a health professional and for that reason Pfizer did not consider it had breached Clause 15.4.

Pfizer submitted that as it had not breached Clause 15.4 of the Code there could not have been a breach of Clauses 2 and 9.1. The contact rate objective for HSRs did not bring discredit upon or reduce confidence in the pharmaceutical industry. In addition, Pfizer submitted that it had maintained high standards at all times because it had mechanisms in place to ensure that health professionals were not inconvenienced and that their wishes were observed.

Pfizer provided the following documents:

1 Performance Plan 2006: This was the formalised list of HSR objectives for the year and put the objective described above in the context of all the other objectives that a manager had agreed with the HSR.

2 Productivity Document: This set out the expectations and measures which would be used to assess performance. These were reviewed quarterly. By way of explanation, the 'Activity' boxes listed the number of daily calls with all customers. The 'target coverage' at the bottom of the page covered the point under consideration, namely the rate at which HSRs were expected to make some form of contact with targeted health professionals in a year.

Pfizer submitted that in addition, it could be seen from the material that the contact rate area of activity was covered under the title 'customer focus'. Customers' wishes must therefore be observed if this objective was to be met. (Again, this highlighted Pfizer's compliance with Clause 15.4).

3 Business Planning Guidance 2006-Anti-Infectives: This document gave guidance on, *inter alia*, how objectives were set. It gave background to each individual set of objectives.

Pfizer submitted that all contact rate targets were agreed jointly between HSRs and their manager. A variety of factors were taken into consideration when agreeing the activity levels which Pfizer expected from its HSRs. Broadly these were: geography and size of a territory, local benchmarking data for other pharmaceutical companies, together with other internal factors such as the number of days an HSR had available for making contact with health professionals which must be balanced with other duties such as training or coaching of new HSRs.

Pfizer submitted that an HSR's contact rate was measured by electronic records of contacts with customers along with a description of the nature of the contact, the time and venue, the information exchanged, the materials used, any particular outcomes and any specific plans for further contact. The records were used in the regular review meetings which an HSR had with their manager.

Pfizer submitted that an HSR could not lose their job solely over contact rates. The contact rates on targeted customers formed only one part of this one objective, which, accounted for 30% of an HSR's total objectives for a whole year. Failure to achieve on a single part of one objective or indeed on a whole objective would not ordinarily constitute grounds for dismissal.

Pfizer submitted that an HSR, just like any other employee of Pfizer, agreed their objectives with their manager at the beginning of the performance planning period and had the right to challenge targets which they considered might be impossible to meet. There were four performance reviews each year at which concerns could be raised at any time in a formal setting. Concerns could also be raised informally at any time by an HSR with their manager. In addition, a concern could also be escalated at any time to senior management through Pfizer's open door policy.

The Business Planning Guidance 2006 – Anti-Infectives document referred to above reflected the point that this objective was one which was to be agreed between an HSR and their manager as it stated the 'frequency [of contact was] to be planned by sales person and agreed with [district sales manager] DSM'.

No Pfizer employee was expected to accept accountability for objectives with which they disagreed or which they believed they would not be able to achieve. Indeed, not all HSRs would have identical contact rate objectives. Experience and geographical considerations, for instance, were considered as outlined above. Again an HSR would have the opportunity, just like any other Pfizer

employee, to challenge the achievability of their objectives.

In conclusion Pfizer did not believe that the contact rate set for HSRs breached Clauses 2, 9.1 or 15.4 of the Code. Pfizer submitted that the objectives set for its HSRs were within the spirit of the Code, particularly because the term 'contact' was interpreted very widely (as set out above and it was not aware of receiving any complaints from hospital health professionals that the frequency of an HSR's contacts had caused them any inconvenience. No *prima facie* case had therefore been established.

PANEL RULING

The Panel noted that the supplementary information to Clause 15.4 stated, *inter alia*, that the number of calls made on a doctor or other prescriber by a representative each year should not normally exceed three on average. This did not include attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up report of an adverse reaction, all of which could be additional to the three visits allowed. Clause 15.4 of the Code referred to representatives ensuring that the frequency, timing and duration of calls and the manner in which they were made did not cause inconvenience.

The Panel noted that according to the documentation HSRs were expected to see senior targets 6.5 times in face to face meetings during the period December 2005-November 2006. The 'overachieved' level was 7.5 face to face meetings. With regard to coverage and frequency, representatives were instructed to 'maintain a robust list of … target doctors and maintain a call rate of 8'. Reference was made to 'Exceeded = Coverage of 95% targets x 8+'.

The Business Planning Guidance 2006 Anti-Infectives identified various customer groups and stated that the coverage was 90% and the frequency 8. A footnote stated that the frequency was to be planned by the representative and agreed with the DSM. Not all the customer groups listed were prescribers. The supplementary information to Clause 15.4 of the Code referred to calls on prescribers.

The Panel noted Pfizer's submission that 'call rate' meant 'contact rate'. This was not clear from the enclosures provided by Pfizer. This wording would be altered. In the Panel's view call rate meant a proactive call from a representative on a health professional and would not be interpreted to mean a call responding to a request or an encounter at a meeting or in a corridor.

The Panel noted Pfizer's submission that its representatives were well trained on the Code but nonetheless considered that the documents needed to stand alone.

The Panel noted that the documents did not give any details about the requirements of the Code nor was the reader referred to the Code. However, regardless of any reference to the Code and its requirements, the Panel considered that in setting the activity targets so high in relation to call rates, the documents advocated a course of action which would be likely to lead to a breach of the Code. This would be a consequence of following the documentation. Thus the Panel ruled a breach of Clause 15.4. The Panel did not consider that the circumstances justified a ruling of a breach of Clause 9.1 of the Code. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved as a sign of particular censure.

Complaint received	**2 August 2006**
Case completed	**6 November 2006**

CASE AUTH/1884/8/06

HOSPITAL CHIEF PHARMACIST v SERVIER

Conduct of representative

A hospital chief pharmacist complained on behalf of an NHS trust about the activities of a Servier representative promoting Protelos (strontium ranelate).

The complainant made a number of allegations concerning: repeated and frequent requests for time with a consultant; provision of biscuits and other snacks for secretarial staff in order to gain access to the consultant; interrupting the consultant during an outpatient clinic; promotion of Protelos to junior medical and ward staff; obtaining clinical details of an inpatient; repeated requests to seek an appointment with the complainant, when the representative was told that the complainant did not see company representatives; entering clinical areas of the hospital uninvited to obtain names of pharmacists to contact later and on refusal of an appointment with the medicines management pharmacist, going to the ward on which this pharmacist routinely worked to find her to promote Protelos.

The Panel noted that the number of contacts with the consultant in the twelve months prior to the representative being asked not to visit the trust (6 proactive calls, 3 at the consultant's request and 2 chance encounters) exceeded that permitted by the supplementary information to the Code. A breach of the Code was ruled as acknowledged by Servier.

The provision of biscuits and snacks for secretarial staff in order to gain access to health professionals was contrary to the Code which prohibited the use of inducements to gain an interview. A breach of the Code was ruled as acknowledged by Servier.

The Panel noted that the representative had visited an outpatient clinic to see the consultant at the end of July 2006. The Panel noted that the parties' accounts of this visit differed. The complainant stated that the visit was in the middle of an outpatient clinic whilst the company stated that the representative arrived after the last patient had left. The complainant understood that the representative had asked to discuss clinical details of a hospital inpatient. Servier denied this stating that the request was to discuss the management of geriatric inpatients. Given these differing accounts the Panel considered that it was not possible to determine whether on the balance of probabilities the representative's conduct amounted to breaches of the Code and thus no breach was ruled.

With regard to the allegation that the representative had promoted Protelos to junior medical and ward staff who had subsequently pressurised the ward consultant, the Panel noted that the complainant did not identify those grades of ward staff that had been promoted to. The Panel was concerned that the representatives' training material referred to student nurses, auxiliary nurses and medical students and did not differentiate between contact with these and more senior staff such as consultants. Despite its concerns about the briefing material and in the absence of further information from the complainant, the Panel did not know to whom the product had been promoted or the hospital policy in this regard. No breach of the Code was ruled.

With respect to the allegation that the representative had obtained details of a hospital inpatient, the Panel noted that the parties' accounts differed. Servier denied the allegation. The complainant had not responded to the Panel's request for further information. It was impossible to determine where the truth lay. No breach of the Code was ruled.

Similarly, in relation to the allegation that the representative had sought appointments with the complainant despite knowing that she did not see representatives, the parties' accounts differed. The Panel did not know where the truth lay and thus ruled no breach of the Code.

In relation to the allegation that the representative had entered clinical areas of the hospital uninvited and obtained names of pharmacists, the Panel considered that whether such conduct was ever acceptable in the absence of a clear invitation to do so would depend, *inter alia*, on the hospital policy. The Panel was concerned that the representatives' briefing document whilst instructing representatives to enter ward areas and such like did not provide any advice on the relevant requirements of the Code. The Panel noted that the acceptability of the representatives' briefing material was the subject of a separate complaint, Case AUTH/1906/10/06. Without further information from the complainant the Panel considered that there was insufficient evidence to establish whether, on the balance of probabilities, such conduct was contrary to either hospital policy, or any direction from those health professionals concerned, to establish breaches of the Code. No breach was ruled.

In relation to the attempts to see the medicines management pharmacist, the Panel noted that the parties' accounts differed. The Panel also noted its comments above about the existence of a hospital policy and activity in clinical areas. It was impossible to determine where the truth lay. The Panel ruled no breach of the Code.

The Panel noted its rulings of breaches of the Code above in relation to call rates and the provision of biscuits and snacks for secretarial staff. The Panel was concerned about the activities of the representative. High standards had not been maintained. A breach of the Code was ruled. Nonetheless the Panel considered that overall, the circumstances did not warrant a ruling of a breach of Clause 2 which was reserved for particular censure.

A district general hospital chief pharmacist complained on behalf of an NHS trust about the way in which a representative of Servier Laboratories Limited promoted Protelos (strontium ranelate).

COMPLAINT

The complainant alleged the following against the representative:

- Repeated and frequent requests for time with a consultant rheumatologist. These requests and just bumping into the consultant outside her office appeared to be more frequent than just by chance.
- Provision of gifts of biscuits and other snacks for secretarial staff in order to gain access to the consultant.
- Requests for the consultant to give the representative two minutes of her time whilst she was in the middle of an outpatient clinic. This request was to discuss clinical details of an inpatient from ward 10 of the hospital which was highly inappropriate.
- Direct promotion of Protelos to junior medical and ward staff. The consultant of this ward was subsequently pressurised to prescribe this medicine. Promotion of a medicine in this way was unacceptable to the organisation.
- Obtaining clinical details of a hospital inpatient.
- Repeated requests for an appointment with the complainant, the chief pharmacist, even though the representative was told that she did not see company representatives.
- Entering the clinical areas of the hospital uninvited and obtaining names of pharmacists whom he later tried to contact.
- On refusal of an appointment with the medicines management pharmacist, going to the ward on which this pharmacist routinely worked to find her and to discuss and promote Protelos.

The trust alleged that the representative was in breach of the Code, particularly with regard to the handling of appointments with health professionals within the trust. The representative had used inducements to try to gain appointments and the frequency and duration of his calls had caused a great deal of inconvenience. He had inappropriately promoted Protelos to junior medical and nursing staff and had used specific patient details in his conversations with consultants.

The complainant had met the representative in July and informed him that he was no longer permitted to visit the trust.

When writing to Servier, the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2, 15.3, 15.4 and 15.9 of the Code.

RESPONSE

As soon as Servier knew of these serious allegations, the representative was suspended pending detailed further investigation and appropriate resolution of the complaint. As a direct result of Servier's investigations, the representative was undergoing a disciplinary procedure. Every aspect of the representative's conduct in this matter had been comprehensively investigated. Servier confirmed that serious disciplinary action would be taken against the representative and that he might be dismissed from the company.

Call frequency

The representative recorded a total of eleven contacts with the consultant in question in the 12 months prior to being asked not to visit the trust by the complainant. Of these calls six were proactive, three were at the request of the consultant to deliver requested data and two were chance encounters in the corridor of the hospital, with no discussions. Servier accepted that this proactive call rate was more frequent than permitted by the Code and regretted any inconvenience that this and the manner in which they occurred had caused the consultant. As a result, Servier accepted a breach of Clause 15.4 of the Code.

Provision of biscuits and snacks

The representative had in the past provided biscuits and snacks for secretarial staff. Servier knew that this might have been an issue earlier in 2006 and so on 15 March 2006 it told all field based staff that this was not acceptable activity (a copy of the memorandum was provided). Since then the representative had not provided snacks etc and his expense claims had been audited to ensure compliance. In light of this Servier accepted that there had been a breach of Clause 15.3 but that clear direction had ensured that this would not happen again.

Outpatient clinic visit

The representative visited an outpatient clinic at the end of July 2006 in order to see the consultant. He arrived in the clinic after the last patient had left. He gave his card to the nurse and asked to see the consultant to discuss the management of elderly patients on a hospital ward. The nurse passed the card to the consultant who said she did not have time to see the representative. He subsequently left. This happened once. At no time during that visit did he discuss or suggest the discussion of an individual patient's clinical details. Servier therefore denied breaches of Clauses 15.2, 15.3 or 15.4.

Clinical details of a patient

Servier noted that the complainant had twice alleged that the representative had obtained clinical details of inpatients. Servier had questioned the representative in detail and was convinced that he never had requested access to individual patient details. The representative tried to discuss the use of Protelos in general terms with the consultant as it might be relevant to a geriatric inpatient population. This had been prompted at the suggestion of a ward manager but the representative never had access to individual patient details. The representative and Servier were fully aware that it was totally inappropriate for a representative to have or request access to such records. Servier did not consider that there was any evidence to support a breach of Clause 15.2.

Promotion of Protelos to junior medical and ward staff

Servier noted that the complainant did not explain why the promotion of Protelos to junior medical staff and ward staff was unacceptable to the trust. It was legitimate for a representative to promote a product to health professionals that included ward staff and junior medical staff under Clause 1.1 of the Code. There was no evidence that the representative was able or tried to get these staff to pressurise the

consultant. In the absence of such evidence or a clearly written or communicated policy and given that the activity was legitimate, there had been no breach of the Code.

Requests to see the complainant

Servier stated that the representative tried to contact the complainant twice between January 2005 and July 2006. Whilst he was unable to secure an appointment on either occasion he was not told that the complainant did not see representatives. In light of this, two attempts to obtain an appointment with a key health professional in the trust in a 19 month period was not inappropriate and was not of a frequency liable to cause inconvenience. Servier did not believe that there had been a breach of Clauses 15.2 or 15.4.

Entering clinical areas

Neither Servier nor the representative knew of a trust policy or direction that representatives should not enter a clinical area of the hospital without permission. Without such direction it was not inappropriate for this to happen provided that the work of the clinical area or patient care was not interfered with or compromised.

Hospital pharmacists were key health professionals and were important contacts for representatives. Obtaining the names of this key group was important and to ask members of staff in clinical areas was not inappropriate. In addition, contacting pharmacists to arrange appointments was not inappropriate in the absence of a direction or policy to the contrary. Neither direction nor policy existed within the trust to Servier's knowledge.

Servier did not accept that this action was inappropriate or in breach of the Code including Clauses 15.2 and 15.4.

Medicines management pharmacist

The representative attempted to contact the medicines management pharmacist through an enquiry at the pharmacy; he was told that she was on the ward. He subsequently went to the ward to attempt to discuss the possibility of an appointment. Unfortunately the pharmacist was not on the ward and so the representative left having neither talked to nor obtained an appointment. Servier did not believe that there was anything inappropriate in these actions especially in the absence of direction or a clear trust policy. Servier submitted that there had therefore been no breach of the Code, including Clauses 15.2 and 15.4.

Briefing Documents

In the 12 months prior to the complaint the representative's team was asked to have twelve 1:1 calls with rheumatologists. This was reflected in a PowerPoint presentation. During this 12 month period, Protelos was a new medicine in the immediate post launch period with a considerable amount of new evidence being published, including the presentation of bone biopsy data. At this time physician experience with Protelos was extremely limited for a chronically prescribed new chemical entity with long-term treatment outcomes. In addition, during this period it was anticipated that there would be a number of formulary decisions being made in the field of osteoporosis. In light of these considerations, Servier set the target to include proactive calls as well as calls to deliver new data at the request of the clinician and data to support the formulary process as requested by the clinician.

The briefing material in the form of a PowerPoint presentation told representatives how to behave in hospitals (a copy was provided) ie in an appropriate manner and to ensure that they complied with hospital regulations.

The representative was under review for under performance primarily as a result of the quality of his interaction with health professionals and not because of call frequency. He was therefore not encouraged to breach the Code with respect to call frequency or through inappropriate behaviour. Servier took the Code with the utmost seriousness and would not encourage or sanction any activity that would be likely to lead to a breach. Servier therefore did not consider that it had breached Clause 15.9.

This representative's activity had not been consistent with Servier's clear instruction given to him to ensure his activity did not breach the Code. Whilst Servier accepted that there had been some failings of this individual, it did not believe that it had failed to maintain high standards and thus did not believe there had been a breach of Clause 9.1. Servier also did not believe that the actions of this individual presented a case for the particular censure for bringing discredit upon or reducing confidence in the pharmaceutical industry and thus there was no breach of Clause 2.

Issues following investigation

Servier had conducted an extensive investigation into the activities of the representative with specific reference to the hospital. As a result of this investigation Servier provided details about the use of emails and letters which were in breach of the Code. Details were provided and these were taken up with Servier as a separate complaint, Case AUTH/1889/9/06.

* * * * *

The complainant was asked on a number of occasions to comment on the points raised by Servier in its response and to advise whether the hospital had a written policy on the conduct of sales representatives and their access to health professionals, to provide a copy of it and to explain how it was disseminated. The complainant did not respond to these requests for additional information.

* * * * *

PANEL RULING

The Panel noted that Clause 15 required, *inter alia*, that representatives must at all times maintain a high

standard of ethical conduct (Clause 15.2) and not employ any inducement etc to gain an interview (Clause 15.3). Representatives should ensure that the frequency, timing, duration of calls and the manner in which they were made did not cause inconvenience. The wishes of individuals on whom representatives wished to call and the arrangements in force at any particular establishment, must be observed (Clause 15.4). The supplementary information to Clause 15.4 of the Code stated that the number of calls made on a prescriber each year must not exceed 3 on average, excluding group meetings, a call which was requested by the doctor or other prescriber, a call to respond to a specific enquiry or a visit to follow up a report of an adverse event reaction.

The Panel noted that the number of contacts with the consultant in the twelve months prior to the representative being asked not to visit the trust (6 proactive calls, 3 at the consultant's request and 2 chance encounters) exceeded that permitted by the supplementary information to Clause 15.4 of the Code. A breach of Clause 15.4 of the Code was ruled as acknowledged by Servier.

The provision of biscuits and snacks for secretarial staff in order to gain access to health professionals was contrary to Clause 15.3 which prohibited the use of inducements to gain an interview. The Panel noted that the company had issued a memorandum clearly stating that such conduct was unacceptable. A breach of Clause 15.3 was ruled as acknowledged by Servier.

The Panel noted that the representative had visited an outpatient clinic to see the consultant at the end of July 2006. The Panel noted that the parties' accounts of this visit differed. The complainant stated that the visit was in the middle of an outpatient clinic whilst the company stated that the representative arrived after the last patient had left. The complainant understood that the representative had asked to discuss clinical details of a hospital inpatient. Servier denied this stating that the request was to discuss the management of geriatric inpatients. Given the parties' differing accounts it was impossible to determine where the truth lay. The Panel considered that the evidence before it was such that it was not possible to determine whether on the balance of probabilities the representative's conduct amounted to a breach of Clauses 15.2 and 15.4 of the Code and thus no breach of these clauses was ruled

With regard to the allegation that the representative had promoted Protelos to junior medical and ward staff who had subsequently pressurised the ward consultant, the Panel noted that the complainant did not identify those grades of ward staff that had been promoted to. The Panel noted that Protelos was indicated for the treatment of postmenopausal osteoporosis to reduce the risk of hip and vertebral fractures. Whilst promotion to health professionals and appropriate administrative staff was permitted the material had to be appropriate and tailored towards the audience (Clauses 1.1 and 12.1). The Panel was concerned that the representatives' training material referred to student nurses, auxiliary nurses and medical students and did not differentiate between contact with these and more senior staff such as consultants. The Panel queried whether given the product's licensed indication it would be appropriate to promote Protelos to, *inter alia*, an auxiliary nurse. Nonetheless, despite its concerns about the briefing material and in the absence of further information from the complainant, the Panel did not know to whom the product had been promoted or the hospital policy in this regard. The Panel thus ruled no breach of Clauses 15.2 and 15.4 of the Code.

With respect to the allegation that the representative had obtained details of a hospital inpatient, the Panel noted that the parties' accounts differed. Servier denied the allegation. The complainant had not responded to the Panel's request for further information. It was impossible to determine where the truth lay. No breach of Clause 15.2 was ruled.

Similarly, in relation to the allegation that the representative had sought appointments with the complainant despite knowing that she did not see representatives, the parties' accounts differed. The Panel did not know where the truth lay and thus ruled no breach of Clauses 15.2 and 15.4 of the Code.

The Panel noted the allegation that the representative had entered clinical areas of the hospital uninvited and obtained names of pharmacists. In the Panel's view, representatives should take great care when entering clinical areas at a hospital. Whether such conduct was ever acceptable in the absence of a clear invitation to do so would depend, *inter alia*, on the hospital policy. The Panel was concerned that the representatives' briefing document whilst instructing representatives to enter ward areas and such like did not provide any advice on the relevant requirements of Clauses 15.2 and 15.4 of the Code. The Panel noted that the acceptability of the representatives' briefing material was the subject of a separate complaint, Case AUTH/1906/10/06. Nonetheless without the benefit of further comment from the complainant the Panel considered that there was insufficient evidence to establish whether, on the balance of probabilities, such conduct was contrary to either hospital policy or any direction from those health professionals concerned to establish a breach of Clauses 15.2 or 15.4 of the Code. No breach was ruled accordingly.

In relation to the attempts to see the medicines management pharmacist, the Panel noted that the parties' accounts differed. The Panel also noted its comments above about the existence of a hospital policy and activity in clinical areas. It was impossible to determine where the truth lay. The Panel ruled no breach of Clauses 15.2 and 15.4 of the Code.

The Panel noted its rulings of breaches of the Code above in relation to call rates and the provision of biscuits and snacks for secretarial staff. The Panel was concerned about the activities of the representative. High standards had not been maintained. A breach of Clause 9.1 was ruled. Nonetheless the Panel considered that overall, the circumstances did not warrant a ruling of a breach of Clause 2 which was reserved for particular censure.

Complaint received **21 August 2006**

Case completed **16 January 2007**

ROCHE v PROCTER & GAMBLE and SANOFI-AVENTIS

Disparagement of Bonviva

Roche complained that, in a concerted campaign, Procter & Gamble and Sanofi-Aventis (the Alliance for Better Bone Health) had consistently misled clinicians about the indication for Roche's product Bonviva (ibandronate) and disparaged the product and the existing evidence base. Procter & Gamble and Sanofi-Aventis supplied Actonel (risedronic acid).

Roche explained that the companies had agreed that the claim 'Only 18% of osteoporotic fractures are vertebral…' was potentially misleading, however the revised claim 'Only 14% of symptomatic osteoporotic fractures are vertebral' (which appeared in a leavepiece and on exhibition panels for Actonel) was also misleading and an unbalanced representation of the data. By only referring to symptomatic vertebral fractures, the burden of vertebral osteoporosis and attendant fractures was grossly underestimated. The vast majority of vertebral fractures were un-diagnosed and yet could have serious clinical consequences at a later date. The lifetime risk of spinal and hip fractures in women was 29% and 14% respectively and in the UK the annual incidence of spinal fractures was 810,000 compared to 400,000 hip fractures (Harvey *et al* 2005). Although the immediate impact of these fractures varied, with 100% of hip fractures, but only 2-10% of vertebral fractures requiring hospitalization, the relative survival rates were similar (0.82 to 0.83).

Whilst the claim might be substantiable, it placed undue emphasis upon a subset of vertebral fractures (those that were symptomatic and came to medical attention), despite the fact that the treatment of the condition depended on diagnosis of osteoporosis, whether or not it was symptomatic. This was unbalanced and misled by implication.

The Panel noted that the claim at issue was referenced to a NICE technology appraisal document on, *inter alia*, alendronate and risedronate for the secondary prevention of osteoporosis fragility fractures in postmenopausal women. This described osteoporosis and noted that fragility fractures occurred most often at the vertebrae, hips and wrists although many vertebral fractures were asymptomatic. Of the estimated 180,000 symptomatic osteoporotic fractures annually in England and Wales, 39% were of the hip, 14% were vertebral fractures and 23% were fractures of the wrist. In women over 50 years of age, the lifetime risk of vertebral fracture was estimated to be about one in three (including asymptomatic vertebral fractures), and approximately one in six for hip fracture. Postmenopausal women with an initial fracture were at much greater risk of subsequent fractures.

The page of the leavepiece at issue included the claim 'Patients would want their osteoporosis treatment to protect them from hip fracture…'. The Panel considered that the page implied symptomatic fractures were either vertebral or hip. No mention was made of wrist fractures (23%). The Panel noted that although the incidence of symptomatic vertebral fractures was less than that of hip fracture, women over 50 were twice as likely to sustain a vertebral fracture (including asymptomatic vertebral fractures) than a hip fracture. The Panel considered that the claim 'Only 14% of symptomatic osteoporotic fractures are vertebral' was misleading as alleged. It minimised the impact of vertebral fractures and implied that they were not very common which was not so. A breach of the Code was ruled.

Roche complained that at a symposium sponsored by Procter & Gamble and Sanofi-Aventis, a slide used by one of the presenters asserted that ibandronate increased the risk of non-vertebral fractures in a subset of patients. This conclusion had been reached by using an inappropriate method of analysis. A more appropriate statistical method revealed that ibandronate did not increase the risk of such fractures. Further, regulatory authorities granted marketing authorization on the basis of anti-fracture efficacy at one skeletal site, and no detrimental effect upon other sites. Thus this claim was not consistent with the Bonviva summary of product characteristics (SPC) and hence disparaged the product.

The Panel noted that the slide in question, headed 'Beware of subgroup analyses!' had been used by an independent speaker at a symposium organized by the Alliance for Better Bone Health. The slide featured two bar charts; the first showed that in patients with a femoral neck BMD > –3.0, ibandronate increased fracture risk by 44% compared with placebo. The second bar chart showed a 64% decreased fracture risk compared with placebo in patients with a femoral neck BMD of < –3.0.

The slide illustrated the dangers of sub-group analysis. The Panel understood that the results shown, if true, might have been such as to prevent Bonviva obtaining a marketing authorisation for the treatment of osteoporosis at least in a subgroup of patients. The Panel acknowledged the very limited use of the data and the context in which the slide was shown but nonetheless considered that Bonviva had been disparaged as alleged. A breach of the Code was ruled.

Roche noted that a telephone survey conducted on behalf of Procter & Gamble and Sanofi-Aventis asked patients to choose between a weekly bisphosphonate with efficacy against both hip and vertebral fractures, and a monthly bisphosphonate with only vertebral fracture efficacy. As Bonviva was the only monthly bisphosphonate, this survey unambiguously referred to ibandronate. The options presented to participants were unbalanced and misleading in that they failed to highlight the fact that both Bonviva and Actonel had similar licences for the treatment of postmenopausal osteoporosis (although different evidence bases) and that there was clinical efficacy for Bonviva at the hip represented by the BMD and bone marker data.

In real life (as opposed to the choices in the questionnaire) Bonviva patients would be given a

patient information leaflet (PIL) which stated 'Bonviva is prescribed to you to treat osteoporosis. Osteoporosis is a thinning and weakening of the bones which is common in women after the menopause…'. There was no warning in the PIL about lack of effect at the hip. The PIL also stated that Bonviva 'prevents loss of bone from osteoporosis and help to rebuild bone. Therefore Bonviva makes bone less likely to break'. To therefore imply in the questionnaire that ibandronate had only vertebral efficacy contradicted the position of the regulatory authorities and prior rulings by the Panel, as well as the general understanding of osteoporosis, the mechanism of action of bisphosphonates and Bonviva's licensed indication. Furthermore, one could only imagine how disquieting such suggestions might be for participants.

Roche alleged that the survey was misleading and disparaging and constituted disguised promotion. It was particularly worrying that this information went directly to patients who were unlikely, unless already treated with Bonviva, to be fully informed of the facts about the efficacy of the medicine. Roche alleged that the survey brought discredit upon, and reduced confidence in, the pharmaceutical industry in breach of Clause 2.

The Panel noted that in the screening questionnaire, all patients currently taking, *inter alia*, Bonviva, were ineligible to take part in the main survey. Thus no patients taking a monthly bisphosphonate would take part.

The main survey sought to elicit perceptions of bisphosphonates with different characteristics. First of all patients had to choose between product R and product I. Product R was to be taken once weekly and had clinical data to show that it reduced fracture at the hip and spine. Product I was to be taken once a month and had clinical data to show that it reduced fracture at the spine but no such data for the hip. Participants were then asked to rate product E, which was a once monthly bisphosphonate which had clinical data to show that it reduced fracture at the spine and hip, and compare it with product R.

The Panel noted that the only requirement in the Code with respect to market research was that such activities must not be disguised promotion. Although the Panel assumed that products I and R were ibandronate (Bonviva) and risedronate (Actonel) respectively, the public would not generally make such an assumption. The Panel did not consider that the questionnaire was disguised promotion of a medicine. No breach of the Code was ruled.

Roche Products Limited complained that Procter & Gamble Pharmaceuticals UK Ltd and Sanofi-Aventis, acting as the Alliance for Better Bone Health, had misled clinicians about the indication for ibandronate (Roche's product Bonviva) and disparaged the product and the existing evidence base. The consistency of this theme across several promotional items and at a recent satellite symposium at the National Osteoporosis Society meeting led Roche to conclude that these actions represented a concerted campaign. Procter & Gamble and Sanofi-Aventis supplied Actonel (risedronic acid).

General Comments by Roche

Roche contended that these efforts undertaken by the Alliance were contrary to the fact that Bonviva had been licensed for the treatment of postmenopausal osteoporosis. This position also contradicted the rulings in Cases AUTH/1779/11/05, AUTH/1780/11/05 and AUTH/1790/1/06. Roche had been satisfied that claims relating to the definition of osteoporosis and the interpretation of the licences of bisphosphonates had been clarified at the completion of these cases. However, the Alliance persisted in claiming, implying and suggesting that Bonviva possessed a restricted licence in osteoporosis that limited its efficacy only to one skeletal area. The Alliance was involved in two of these appeals and thus would know about the Appeal Board's rulings.

Roche noted that Bonviva was licensed for the treatment of osteoporosis in postmenopausal women, in order to reduce the risk of vertebral fractures. Demonstration of a reduction in the rate of femoral neck fractures was not a requirement for the licence of treatment of postmenopausal osteoporosis. Osteoporosis was a generalised disease of bone. Bisphosphonates acted on all bones. In addition section 5.1 of the Bonviva summary of product characteristics (SPC) under the heading of 'Clinical efficacy' showed that Bonviva increased bone mineral density (BMD) at the whole hip, the femoral neck and trochanter. In addition this section stated that Bonviva produced 'clinically meaningful reductions in markers of bone resorption'.

Roche had detailed in the above cases that the EU requirements for obtaining an osteoporosis licence took account of the problems involved in carrying out placebo-controlled studies for new bisphosphonates. These guidelines also stated that a licence for osteoporosis would only be granted if anti-fracture efficacy had been demonstrated at a minimum of one site, with no deleterious effect upon other sites. The same guidelines indicated that licences were issued for either the treatment or prevention of postmenopausal osteoporosis. Marketing authorization for the treatment of osteoporosis was not granted in a site-specific manner. A claim that Bonviva reduced fracture rates at the hip would not be consistent with the SPC. Conversely claims that Bonviva had no effect at the hip (ie ignoring the BMD data) or that its pharmacodynamic effect was restricted to vertebral bone were misleading, unbalanced, unfair and inaccurate.

These matters had previously been addressed through inter-company dialogue and with the Authority. Nevertheless, the Alliance continued to disparage the efficacy and safety profile of ibandronate. Despite inter-company communication, Roche was unable to reach a consensus, and thus was obliged to refer the matter to the Authority.

1 Claim 'Only 14% of symptomatic osteoporotic fractures are vertebral'

This claim appeared as the heading to an Actonel

leavepiece (A2925) and also on exhibition panels.

COMPLAINT

Roche noted that during inter-company discussion, it had been agreed that the claim 'Only 18% of osteoporotic fractures are vertebral…' was potentially misleading. However Roche considered that the revised claim 'Only 14% of symptomatic osteoporotic fractures are vertebral' was also misleading and an unbalanced representation of the data. By only referring to vertebral fractures which presented to medical attention symptomatically, the burden of disease imposed by vertebral osteoporosis and attendant fractures was grossly underestimated. It was well known that the vast majority of vertebral fractures were un-diagnosed and yet could have serious clinical consequences at a later date. In contrast, Harvey *et al* (2005) revealed that the lifetime risk of spinal and hip fractures in women was 29% and 14% respectively. The authors also reported that in the UK, the annual incidence of spinal fractures was 810,000 compared to 400,000 hip fractures. Although the immediate impact of these fractures varied, with 100% of hip fractures, but only 2-10% of vertebral fractures requiring hospitalization, the relative survival rates were similar (0.82 to 0.83).

All information in promotional material must be accurate and balanced. Whilst the claim might be capable of substantiation, the statement placed undue emphasis upon a subset of vertebral fractures (ie those that were symptomatic and came to medical attention), despite the fact that the treatment of the condition depended on diagnosis of osteoporosis, whether or not it was symptomatic. This was unbalanced and misleading by implication and in breach of Clause 7.2.

RESPONSE

Procter & Gamble and Sanofi-Aventis stated that they had talked to Roche about a related claim, 'In established osteoporosis only 18% of osteoporotic fractures are vertebral', and as a conciliatory gesture had offered to amend it. Roche had not discussed the revised claim with the companies, which was not in the spirit of the process described above.

The 14% cited in this leavepiece was derived from, and thus substantiated by, data published by the National Institute for Health and Clinical Excellence (NICE). The leavepiece was intended for doctors who based the diagnosis of osteoporosis on clinical evidence. Procter & Gamble and Sanofi-Aventis agreed that the treatment of the condition depended on the diagnosis of osteoporosis. Current NICE guidance referred to women who had sustained a clinically apparent osteoporotic fracture, thus emphasizing the role of the symptomatic osteoporotic fracture in treatment decisions. In the Appraisal Consultation Document issued by NICE on the primary prevention of osteoporotic fragility fractures, treatment decisions were guided by the result of BMD measurement and additional risk factors, none of which included un-diagnosed vertebral fractures. Thus when talking to physicians it made sense to refer to clinical/symptomatic vertebral fractures specifically, as these were the fractures that came to clinical attention, resulting in consultations and subsequent costs to the NHS.

In addition, Roche had referred to the review by Harvey *et al*; some of the data cited by Roche from that paper was from 1992. The 29% lifetime risk of spinal fracture cited by Roche was actually 28% in the paper and the annual incidence of spinal fracture of 810,000 and of hip fracture of 400,000 did not appear in the paper. While Procter & Gamble and Sanofi-Aventis agreed that the amount of un-diagnosed vertebral fractures was of academic interest, the figure relevant to doctors was the number of fractures coming to clinical attention (namely 14%), which was specifically highlighted in the documents from NICE.

Procter & Gamble and Sanofi-Aventis therefore disagreed that the claim was misleading. The leavepiece was a balanced view of scientific and promotional communication of current data. The companies denied a breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the claim 'Only 14% of symptomatic osteoporotic fractures are vertebral' was referenced to NICE. The NICE document in question was a technology appraisal document on, *inter alia*, alendronate and risedronate for the secondary prevention of osteoporosis fragility fractures in postmenopausal women (January 2005). Section 2, 'Clinical need and practice', described osteoporosis and noted that fragility fractures occurred most often at the vertebrae, hips and wrists although many vertebral fractures were asymptomatic. Of the estimated 180,000 symptomatic osteoporotic fractures annually in England and Wales 39% were hip fractures, 14% were vertebral fractures and 23% were fractures of the wrist. In women over 50 years of age, the lifetime risk of vertebral fracture was estimated to be about one in three (including asymptomatic vertebral fractures), and approximately one in six for hip fracture. Postmenopausal women with an initial fracture were at much greater risk of subsequent fractures.

The page of the leavepiece at issue included the claim 'Patients would want their osteoporosis treatment to protect them from hip fracture…'. The Panel considered that the page implied symptomatic fractures were either vertebral or hip. No mention was made of wrist fractures (23%). The Panel noted that although the incidence of symptomatic vertebral fractures was less than that of hip fracture, women over 50 were twice as likely to sustain a vertebral fracture (including asymptomatic vertebral fractures) than a hip fracture. The Panel considered that the claim 'Only 14% of symptomatic osteoporotic fractures are vertebral' was misleading as alleged. It minimised the impact of vertebral fractures and implied that they were not very common which was not so. A breach of Clause 7.2 was ruled.

2 Use of inappropriate statistical analysis

COMPLAINT

Roche stated that Procter & Gamble and Sanofi-Aventis had been responsible for the claim that

ibandronate increased non-vertebral fracture risk in a subset of patients. At a symposium sponsored by the two companies at the National Osteoporosis Society, a slide used by one of the presenters asserted that ibandronate increased the risk of non-vertebral fractures in a subset of patients from the pivotal BONE study with a femoral neck BMD T-score > –3. This misleading and inaccurate claim would inevitably raise concerns about ibandronate's safety profile.

To arrive at this conclusion, chi-square analyses were applied to data that appeared on the FDA website. Whilst such tests were useful for elucidating differences between groups, this analysis was inappropriate when examining drug effects, which must take 'time to event' into account. To determine drug efficacy therefore, the FDA proposed that Kaplan-Meier tests were performed. This appropriate analysis revealed that ibandronate did not increase the risk of non-vertebral fractures in a subset with femoral neck BMD T-scores > –3.0. Further, it should be acknowledged that the regulatory authorities granted marketing authorization on the basis of anti-fracture efficacy at one skeletal site, and no detrimental effect upon other sites. Thus this claim was not consistent with the Bonviva SPC and hence disparaged the product.

Procter & Gamble and Sanofi-Aventis contended that all the data represented the speaker's opinion. However, it was the sponsor's responsibility to ensure that all materials relating to a sponsored conference symposium were accurate, fair, balanced and neither misleading or disparaging. Furthermore, the supplementary information to Clause 7.2 indicated that there were precedents wherein claims were based upon publications quoting incorrect statistical methodology. Thus, the supplementary information to Clause 7.2 required that 'before statistical information is used … it must be subjected to statistical appraisal'.

RESPONSE

Procter & Gamble and Sanofi-Aventis submitted that the slide was developed by the speaker, in this case an international thought leader in the field of osteoporosis and a former officer of the European Calcified Tissue Society, the key European society for osteoporosis research, who was not an employee of either of the two companies. The two companies had not provided any materials showing a proportional analysis figure of the sub-population in question and the speaker confirmed in his letter to the Authority, that Roche had misrepresented what was actually presented.

The above presentation reflected an independent opinion and in addition conveyed a fair and balanced view of the data supporting ibandronate. Roche had not fairly represented what occurred at the symposium, so Procter & Gamble and Sanofi-Aventis therefore disagreed with the opinion that there had been a breach of Clause 8.1 of the Code.

PANEL RULING

The Panel noted that the slide in question, headed 'Beware of subgroup analyses!' had been used by an independent speaker at a symposium organized by the Alliance for Better Bone Health. The slide featured two bar charts; the first showed that in patients with a femoral neck BMD > –3.0, ibandronate increased fracture risk by 44% compared with placebo. The second bar chart showed a 64% decreased fracture risk compared with placebo in patients with a femoral neck BMD of < –3.0.

The Panel noted that the slide was shown to delegates at a company-sponsored symposium and used to illustrate the dangers of sub-group analysis. The slide featured clinical results about a product which was a direct competitor to that of the sponsor company. The Panel queried why other data could not have been used to illustrate the point. The Panel understood that the results shown, if true, might have been such as to prevent Bonviva obtaining a marketing authorisation for the treatment of osteoporosis at least in a subgroup of patients. The Panel acknowledged the very limited use of the data and the context in which the slide was shown but nonetheless considered that Bonviva had been disparaged as alleged. A breach of Clause 8.1 was ruled.

3 Market research telephone survey

COMPLAINT

Roche alleged that a patient preference survey conducted on behalf of Procter & Gamble and Sanofi-Aventis disparaged Bonviva. The telephone questionnaire asked patients to choose between a weekly bisphosphonate with efficacy against both hip and vertebral fractures, and a monthly bisphosphonate with only vertebral fracture efficacy. As Bonviva was the only monthly bisphosphonate, this survey unambiguously referred to ibandronate. The options presented to participants were unbalanced and misleading in that it failed to highlight the fact that both Bonviva and Actonel had similar licences for the treatment of postmenopausal osteoporosis (although different evidence bases) and that there was clinical efficacy for Bonviva at the hip represented by the BMD and bone marker data.

In real life (as opposed to the choices in the questionnaire) Bonviva patients would be given a patient information leaflet (PIL) which stated 'Bonviva is prescribed to you to treat osteoporosis. Osteoporosis is a thinning and weakening of the bones which is common in women after the menopause…'. There was no warning in the PIL about lack of effect at the hip. The PIL also stated that Bonviva 'prevents loss of bone from osteoporosis and help to rebuild bone. Therefore Bonviva makes bone less likely to break'. To therefore imply in the questionnaire that ibandronate had only vertebral efficacy contradicted the position of the regulatory authorities and prior rulings by the Panel, as well as the general understanding of osteoporosis, the mechanism of action of bisphosphonates and Bonviva's licensed indication. Furthermore, one could only imagine how disquieting such suggestions might be for participants in the survey if they, or someone known to them, were prescribed Bonviva.

Roche alleged that the survey was misleading and

disparaging in breach of Clauses 7.2 and 8.1 and constituted disguised promotion in breach of Clause 10.2. Roche considered that the survey was irresponsible and deliberately disparaged the only available monthly bisphosphonate by implication. It was particularly worrying that this information went directly to patients who were unlikely, unless already treated with Bonviva, to be fully informed of the true facts about the efficacy of the medicine. Roche believed therefore that this activity brought discredit upon, and reduced confidence in, the pharmaceutical industry, and therefore alleged a breach of Clause 2.

RESPONSE

Procter & Gamble and Sanofi-Aventis submitted that the market research was non-promotional and did not contravene the Code.

Procter & Gamble and Sanofi-Aventis noted Roche's allegation that the survey failed to highlight that the licences had similar indications but different evidence bases. The wording in the questionnaire 'The product does not have information based on clinical studies to support that it is effective at reducing the risk of a broken hip bone' referred to the difference in this evidence base.

Roche had also claimed that Actonel and Bonviva had similar licences. Rulings from the Appeal Board clearly stated that the Bonviva indications were not similar to the indications for once weekly bisphosphonates: Cases AUTH/1779/11/05 and AUTH/1780/11/05. In addition the Appeal Board went on to state 'given the context of the page readers would assume that alendronate and Bonviva had the same indication and this was not so'. In Cases AUTH/1790/1/06 and AUTH/1791/1/06, the Appeal Board stated 'Prescribers might be persuaded to change patients from Fosamax Once Weekly to Bonviva in the belief that the evidence base for the indication was the same for each. This was not so; the efficacy of Bonviva on hip fracture had not been established whilst Fosamax was specifically licensed to reduce the risk of hip fracture'.

Roche went on to quote the Bonviva PIL and stated that 'there is no warning in the PIL about lack of effect at the hip'. It was not common practice to include warnings of lack of efficacy in the PIL and this could not be accepted as the position of the regulatory authorities that ibandronate had shown efficacy in hip fracture reduction. On the contrary the regulatory authorities had clearly stated in the indication section of the Bonviva SPC: 'Efficacy on femoral neck fractures has not been established'.

Roche mentioned how disquieting this survey might have been to subjects if they or someone known to them were prescribed ibandronate. In the screening document it was outlined that only subjects currently on a weekly bisphosphonate were eligible to participate. It was also very unlikely that the subjects would be aware that only one monthly treatment existed as promotion direct to consumers was prohibited under the Code.

Based on the above Procter & Gamble and Sanofi-Aventis denied that the telephone survey was in breach of Clauses 2, 7.2 and 10.2. The telephone survey was conducted as pure market research and was not promotional or disparaging to Bonviva.

PANEL RULING

The Panel noted the parties' references to previous cases and was concerned about some of Procter & Gamble and Sanofi-Aventis' comments about the rulings. The previous cases had all involved material directed at health professionals. The matter now under consideration involved material for patients. Each case under the Code had to be considered on its own merits.

The Panel noted that in the screening questionnaire, all patients currently taking, *inter alia*, Bonviva, were ineligible to take part in the main survey. Thus no patients taking a monthly bisphosphonate would take part in the survey.

The main survey sought to elicit patients' perceptions of bisphosphonates with different characteristics. First of all patients had to choose between product R and product I. Product R was to be taken once weekly and had clinical data to show that it reduced fracture at the hip and spine. Product I was to be taken once a month and had clinical data to show that it reduced fracture at the spine but no such data for the hip. Participants were then asked to rate product E, which was a once monthly bisphosphonate which had clinical data to show that it reduced fracture at the spine and hip, and compare it with product R.

The Panel noted that the only requirement in the Code with respect to market research was that such activities must not be disguised promotion. Although the Panel assumed that products I and R were ibandronate (Bonviva) and risedronate (Actonel) respectively, the public would not generally make such an assumption. The Panel did not consider that the questionnaire was disguised promotion of a medicine. No breach of Clause 10.2 was ruled. It thus followed that there was no breach of Clauses 7.2, 8.1 and 2 of the Code.

Complaint received **22 August 2006**

Case completed **8 December 2006**

CASE AUTH/1889/9/06

VOLUNTARY ADMISSION BY SERVIER

Conduct of representative

In its response to Case AUTH/1884/8/06, which concerned the conduct of a representative, Servier referred to the inappropriate use of email and the creation and use of letters by the representative. Servier accepted that such conduct was in breach of the Code. As these matters were not the subject of complaint in Case AUTH/1884/8/06 Servier's comments on these points were regarded as a voluntary admission.

The Authority's Constitution and Procedure stated 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 action to address it.

The use of email for promotional purposes without the prior permission of the recipient and the creation and subsequent use of promotional material by a representative were regarded as a serious matters and the Director decided that the admission must accordingly be treated as a complaint.

The Panel noted that the representative had emailed a hospital doctor inviting her to speak at a meeting and suggesting a lunchtime meeting to discuss Protelos (strontium ranelate). A letter to the same doctor sought to rebook a cancelled appointment to discuss 'new evidence behind Protelos, including unique data looking at Non-Vertebral Fractures in the Over 80s… and the long term data'. The letter concluded with 'Would you recommend for patients unable to take the Bisphosphonates, that Protelos is the next option in line with the formulary?' in emboldened type.

Both the letter and email promoted Protelos. The recipient had not given prior permission for receipt of a promotional email and thus a breach of the Code was ruled as acknowledged by the company. The representative had created and disseminated promotional material contrary to Servier's instructions; each piece ought to have been certified and include prescribing information. The representative had not maintained a high standard of ethical conduct: a breach of the Code was thus ruled.

The Panel examined the training materials and noted that the company had not established that the representative had received any relevant training when the initial email was sent.

The Panel considered that on the evidence before it the instructions to representatives about the creation of promotional material and the use of email for promotion purposes were inadequate; a breach of the Code was ruled. High standards had not been maintained. A breach of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved to indicate particular censure of a company's material or activities.

In its response to Case AUTH/1884/8/06, which concerned the conduct of a representative, Servier Laboratories Ltd referred to the inappropriate use of email and the creation and use of letters by the representative. Such activities were contrary to the company's specific instructions. Servier accepted that such conduct was in breach of the Code. As these matters were not the subject of complaint in Case AUTH/1884/8/06 Servier's comments on these points were regarded as a voluntary admission.

The action to be taken by the Authority in relation to a voluntary admission by a company was set out in Paragraph 5.4 of the Authority's Constitution and Procedure. This stated that the Director should treat the matter as a complaint if it related to a potentially serious breach of the Code or if the company failed to take action to address it.

COMPLAINT

The use of email for promotional purposes without the prior permission of the recipient and the creation and subsequent use of promotional material by a representative was regarded as a serious matter and the Director decided that the admission must accordingly be treated as a complaint.

RESPONSE

Servier explained that, despite company instructions not to do so, the representative in question had used email to contact a doctor; the content of at least one of those emails was promotional. This was unacceptable and in breach of Clause 15.2 and also Clause 9.9 as the recipient did not give permission for such use of email.

In addition to email use, and again contrary to specific instructions, the representative had written letters to doctors that were promotional. These letters did not contain prescribing information and were not certified and thus Servier acknowledged a breach of Clause 15.2.

From the in-house training course it was clear that representatives were instructed in a number of acceptable ways of contacting health professionals in hospitals. This instruction did not include the unsolicited use of emails or letters. Servier took all matters relating to the Code very seriously and noted that the representative in question had been disciplined. Any issues identified by the organisation were dealt with quickly and decisively as was evidenced by a bulletin (provided) dated 15 March 2006. Servier therefore did not accept that there had been a breach of Clauses 9.1 and 15.9.

Servier did not believe that the breaches admitted above brought discredit upon, or reduced confidence in, the pharmaceutical industry as it was an isolated

case of an individual acting against clear direction from the company. Servier did not therefore consider that this warranted a breach of Clause 2.

PANEL RULING

The Panel noted that the representative at issue had emailed a hospital doctor inviting her to speak at a proposed meeting and suggesting a lunchtime meeting to discuss Protelos and data about non-vertebral fractures in the over 80s. A letter to the same doctor sought to rebook a cancelled appointment to discuss 'new evidence behind Protelos, including unique data looking at Non-Vertebral Fractures in the Over 80s… and the long term data'. The letter concluded with the question in an emboldened type face 'Would you recommend for patients unable to take the Bisphosphonates, that Protelos is the next option in line with the formulary?'

The Panel noted that both the letter and email promoted Protelos. The recipient had not given prior permission for receipt of a promotional email and thus a breach of Clause 9.9 was ruled as acknowledged by the company. The representative had created and disseminated promotional material contrary to Servier's instructions; each piece ought to have been certified in accordance with Clause 14.1 and include prescribing information. The representative had not maintained a high standard of ethical conduct: a breach of Clause 15.2 was thus ruled.

The Panel noted that whilst the training course discussed contact with health professionals in a hospital environment it did not mention the unsolicited use of email or creation of promotional material by representatives nor did it refer to any other briefing material which might have covered such issues. The training course was undated and it was thus unclear whether it predated the activities at issue or indeed whether the representative in question had received the training. The bulletin dated 15 March 2006 was sent after the email but before the letter. It discussed the 2006 Code and told representatives not to send promotional emails (ie any which referred to a Servier product) to health professionals and, in a separate bullet point, to 'use only materials that had been approved through the regulatory process.' The Panel queried whether it was sufficiently clear that unapproved promotional letters created by representatives should not be used. There was no cross reference to any document which might have addressed the matter. Some might assume that the term 'materials' in the bulletin referred to normal promotional leaflets, detail aids and suchlike rather than a letter seeking an appointment which included promotional claims. The Panel also noted that the company had not established that the representative had received any training on this point when the initial email was sent.

The Panel considered that on the evidence before it the instructions to representatives about the creation of promotional material and the use of email for promotion purposes were inadequate; a breach of Clause 15.9 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was reserved to indicate particular censure of a company's material or activities.

During its consideration of this case the Panel was extremely concerned about the training material and whether it met the requirements of Clauses 2, 9.1, 15.2, 15.4 and 15.9 of the Code. The Panel decided to take its concerns up with Servier as a separate complaint in accordance with Paragraph 17 of the Constitution and Procedure, Case AUTH/1906/10/06.

Proceedings commenced **13 September 2006**

Case completed **2 November 2006**

CASE AUTH/1890/9/06

CONTRACT REPRESENTATIVE v SERVIER

Representative call rates

A contract representative complained about the call rates set by Servier. The complainant alleged that in September representatives had been asked to see target GPs three times before Christmas but many representatives had less than 50 target doctors and had been requested to see some GPs up to six times before Christmas. The complainant considered that this was highly unreasonable and in breach of the Code as representatives were only allowed three unsolicited calls a year and most target doctors would have already been seen once or twice this year.

The Panel noted that supplementary information to the Code stated that the number of calls made on a doctor or other prescriber each year should not normally exceed three on average excluding attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction.

The Panel noted that on Friday, 15 September, the contract representative agency emailed those of its representatives who did not have 50 target GPs in their territory. Representatives were told that territories with 50 target GPs would need an average call frequency of three in order to achieve one of the key deliverables for the sales project but as their territory had less than 50 targets they would 'be required to see them at increased frequency'. On Thursday, 21 September, after some discussion with Servier, the agency contacted its sales managers to tell them that more doctors would be added to target lists so that overcalling would not be necessary. The Panel was concerned that no written instructions in this regard appeared to have been sent to the field force thus retracting the need for representatives to call on doctors 'at increased frequency'. Notwithstanding any further instructions, the Panel considered that the email sent on 15 September advocated a course of action which was likely to breach the Code. A breach of the Code was ruled.

The Panel noted that there was no evidence that overcalling had actually occurred. No breach was ruled in that regard. A ruling of a breach of Clause 2 of the Code was a sign of particular censure and was reserved for such circumstances. The Panel did not consider that the matter was sufficiently serious to warrant such a ruling.

COMPLAINT

A contract representative working for Servier Laboratories Ltd alleged that in September representatives had been asked to see target GPs three times before Christmas but many representatives had less than 50 target doctors and had been requested to see some GPs up to six times before Christmas. The complainant considered that this was highly unreasonable and in breach of the Code as representatives were only allowed three unsolicited calls a year and most target doctors would have already been seen once or twice this year.

When writing to Servier, the Authority asked it to respond in relation to Clauses 2, 15.4 and 15.9 of the Code.

RESPONSE

Servier stated that in early September 2006 it agreed to purchase detail consultations from a contract representative agency to be filled by contract representatives ideally before 31 December 2006. Each contract representative was to be given a target list of GPs and would be expected to deliver 75% of the expected calls on these targets. There was no overlap between these targets and any GPs targeted by Servier representatives. Of the target list only 73% were indicated by the agency to have the potential or would possibly be willing to see representatives and would therefore be included in the targeting exercise. Of these, 58% had previously been seen by the agency's sales force (pro-actively, at meetings and at the request of the doctor) in the 12 months to September at an average frequency of 2.17, of these 30% were anticipated to have been proactive.

Servier explained that the contract with the agency was for a number contacts of which it was anticipated that 75% would be on target GPs. These contacts were to be delivered by the contract representatives on 50 targets each. This equated to 3 contacts per target on average. The agency anticipated that 30% of these contacts would occur at group meetings of which two out of every three would request further information creating further contacts. This would leave a proactive average contract rate in the 4 month period of just less than 1. Details were provided.

Servier noted that the contacts required from the agency were to be averaged over the target group and not a specific number per target GP.

Servier submitted that it was thus clear that its contract with the agency did not require or advocate breaching the Code. Servier was confident that there had not been a breach of either Clause 15.2 or 15.9.

During a targeting exercise the agency established that ten of its territories had less than the required number of target doctors. The agency asked Servier for direction on this on 13 September.

On the 15 September the agency emailed the affected representatives and suggested that an increased frequency could be one proposal to make up the missing contacts. Servier noted that this was not an instruction. The attached email below this email outlined the targeting process to be carried out by the representatives. This activity was to start on 15 September and be completed at midnight on 18 September. Thus without knowing the actual target lists per territory and without the requested instruction from Servier, the agency was not in a

position to instruct overcalling as alleged. The proposal in the email to the affected representatives was an attempt to acknowledge that some representatives, on commencing the targeting exercise, might be concerned about their lack of targets and that this was being worked on by the agency. Thus a breach of Clause 15.9 did not occur at this time.

Once the targeting had been completed and assessed, the agency emailed Servier with a proposal (not as yet communicated to the representatives) that territories with less than fifty targets be incentivised to overcall. On 21 September in the morning a telephone message was left at the agency to contact Servier urgently to discuss the proposal. At 2.41pm on 21 September Servier told the agency that the proposal was unacceptable and that Servier would increase the target number in these territories to ensure no overcalling. In addition a new incentive scheme was proposed that ensured that overcalling was actively de-incentivised. The details of this were confirmed in a further telephone call at 16.20 on the same day. In between these two calls the agency telephoned its sales managers to tell them that more doctors would be added to the target lists of those affected. At no time did Servier or the agency require representatives to overcall on GPs and thus no breach of Clause 15.9 had occurred. As a result of this, no representative could have overcalled in the six days (including the weekend) where any misinterpretation of information was viewed as an instruction to overcall. Thus no breach of Clause 15.2 had occurred.

Servier provided a copy of a presentation on GP targeting given to the primary care representatives in late September which related to the 12-month period from October 2006. On slide 6 of this presentation the representatives were told to ensure that activity was in line with the Code and this was reinforced in slide 12. Slide 7 outlined the expected number of contacts on each doctor. Each doctor might be on the target list for 2 and sometimes 3 representatives. Past experience of primary care representatives' activity at Servier had suggested that no more than 50% of all contacts were proactive with the rest being either 1:1 requested call backs or contacts at meetings. This therefore did not encourage the representatives to overcall on this group of prescribers and therefore there had been no breach of either Clause 15.2 or Clause 15.9 of the Code.

The presentation given in late September 2006 outlined the expected call rates for primary care representatives. This outlined the expected activity for the 4-month period from October 2006 to the end of January 2007. There were 3 teams of representatives. The reference provided represented the expected activity including proactive calls, requested call backs and meetings. Each doctor might have more than one representative calling on them. In addition, where a GP was on more than one target list a representative would be expected to discuss more than one product in a single call. In light of this and the expected proportion of calls to be proactive, Servier had not briefed the representatives to breach the Code. There had been no breach of Clause 15.9 of the Code.

The secondary care representatives were split into two teams; 'Endocrine' and 'Cardiovascular'. The two teams were briefed differently but both briefings were contained in a presentation given at the end of September 2006. The cardiovascular representatives were asked to have between two and three contacts over the 4-month period between October 2006 and the end of January 2007. In Servier's experience about half of these calls would be group detail or speaker meetings. Another quarter would be requested call backs. The high degree of call back was anticipated due to the post-launch period of one of the key products and the relative lack of knowledge of the clinical data.

The endocrine representatives were asked to have between 2 and 4 contacts over the period from October to the end of January 2007. These contacts would be a mixture of proactive 1:1 calls, meetings and call backs. As above Servier anticipated at least half of these calls would be group detail or speaker meetings with another quarter as call backs. The increased number of contacts mentioned in the brief reflected the fact that a number of presentations would be made to formulary committees due to the stage in the life cycle of the product. It was anticipated that a large number of call backs would arise from these as well as group presentations. Servier considered that there had been no breach of the Code in any of these briefings.

Servier did not consider that any activity described above either with the contract sales team or with the representatives' briefing constituted bringing discredit upon or reducing confidence in the pharmaceutical industry. The company did not therefore consider that there had been a breach of Clause 2 of the Code.

PANEL RULING

The Panel noted that under the Code, Servier was responsible for the activities which the contract representative agency carried out on its behalf.

The supplementary information to Clause 15.4 stated that the number of calls made on a doctor or other prescriber each year should not normally exceed 3 on average excluding attendance at group meetings and the like, a visit requested by the doctor or other prescriber or a visit to follow up a report of an adverse reaction.

The Panel noted that on Friday, 15 September 2006 the agency emailed those of its representatives who did not have 50 target GPs in their territory. Representatives were told that territories with 50 target GPs would need an average call frequency of 3 in order to achieve one of the key deliverables for the sales project but as their territory had less than 50 targets they would 'be required to see them at increased frequency'. On Thursday, 21 September, after some discussion with Servier, the agency contacted its sales managers to tell them that more doctors would be added to target lists so that overcalling would not be necessary. The Panel was concerned that no written instructions in this regard appeared to have been sent to the field force thus retracting the need for representatives to call on doctors 'at increased frequency'. Notwithstanding

any further instructions, the Panel considered that the email sent on 15 September advocated a course of action which was likely to breach the Code. A breach of Clause 15.9 was ruled.

The Panel noted that there was no evidence that overcalling had actually occurred. No breach of Clause 15.4 was ruled.

A ruling of a breach of Clause 2 of the Code was a sign of particular censure and was reserved for such circumstances. The Panel did not consider that the matter was sufficiently serious to warrant such a ruling.

Complaint received	**20 September 2006**
Case completed	**24 November 2006**

CASE AUTH/1891/9/06

VOLUNTARY ADMISSION BY LILLY

Articles in the lay press

Lilly advised the Authority that a freelance journalist whom it had sponsored to attend the European Society of Sexual Medicine (ESSM) Conference in December 2005, had written two articles about Cialis (tadalafil) in the lay press. An article in Take a Break magazine, March 2006, referred to Lilly's erectile dysfunction (ED) disease awareness campaign and also included a pack shot of Cialis. The second article, which appeared in the June 2006 edition of Choice magazine, also referred to Cialis and included a patient's history with regard to erectile dysfunction. Both articles featured quotations from a doctor. The Authority's Constitution and Procedure required the Director to treat a voluntary submission as a complaint if, *inter alia*, it related to a potentially serious breach of the Code.

The possible promotion of a prescription only medicine to the public was regarded as a serious matter and the Director thus decided that Lilly's voluntary admission must accordingly be treated as a complaint.

The Panel noted that the two articles discussed ED, its causes and treatment. The article in Take a Break focussed on the condition in younger men, the other featured a more detailed discussion of ED and Cialis trial data with particular emphasis on a continuous daily dosing regime which was currently strongly discouraged as the long-term side effects after prolonged use had yet to be studied. The article in Choice magazine specifically referred to the proceedings at ESSM.

The Panel noted that Lilly had invited the journalist to and sponsored her attendance at ESSM in December 2005. The itinerary provided to the journalist by Lilly described presentations about ED and general issues in sexual medicine as optional but the Lilly ICOS symposium 'ED and Beyond – Lessons to Learn from the Past for the Future' as compulsory. The symposium included a podium session on the unlicensed dosage regimen of Cialis once daily everyday. The media interview with the doctor (who was later quoted in the two articles) was listed as a compulsory event. The Panel noted that Lilly had arranged the interview at the journalist's request although she had run the interview. Whilst the Panel noted Lilly's submission that neither it nor its affiliates or PR agency had provided any material to the journalist, the company had, nonetheless, made attendance at the Cialis symposium compulsory. The Panel considered that irrespective of whether Lilly had provided any material to the journalist it should have satisfied itself that the content of the Lilly symposium was appropriate for the journalist in relation to the Code. The Panel noted that the company had amended its SOPs to ensure that all such meetings held outside the UK would be certified.

The Panel noted that the journalist had contacted the doctor she had interviewed at the conference some time later with more questions about ED. Lilly had given the doctor general media advice. The conference had taken place in December 2005 and the first of the articles in question was published in March 2006.

The Panel considered that there was no evidence that Lilly had provided any information or material to the journalist which was inconsistent with the Code and accordingly ruled no breach of the Code. The Panel noted that Lilly had arranged for the journalist to attend a clinical symposium at which Cialis would be discussed; there was particular focus on the use of continuous once daily treatment. The article in Choice magazine had specifically referred to proceedings at ESSM. The Panel could not understand why Lilly had arranged for the journalist's attendance at ESSM, insisted that she attend the company sponsored symposium and then asked her not to write about it. On balance the Panel considered that Lilly had provided the journalist with information that would encourage patients to ask their doctor to prescribe Cialis. A breach of the Code was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2.

COMPLAINT

Lilly advised the Authority that a freelance journalist whom it had sponsored to attend the European Society of Sexual Medicine (ESSM) Conference in December 2005, had written two articles about Cialis (tadalafil) in the lay press. The first article appeared in Take a Break magazine March 2006 and referred to www.lovelifematters.co.uk, Lilly's erectile dysfunction (ED) disease awareness campaign and also included a pack shot of Cialis. The second article which appeared in the June 2006 edition of Choice magazine also referred to Cialis and included a patient's history with regard to ED. Both articles featured quotations from a doctor.

The Authority's Constitution and Procedure stated 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 action to address it.

The possible promotion of a prescription only medicine to the public was regarded as a serious matter and the Director thus decided that Lilly's voluntary admission must accordingly be treated as a complaint.

When writing to Lilly, the Authority asked it to respond in relation to Clauses 2, 20.1 and 20.2 of the Code.

RESPONSE

Lilly explained that it did not request, mandate or pay the journalist to write either article and had not approved their content. Once the company knew about these articles it asked the journalist not to write further articles about Cialis based on the information she had gathered at ESSM.

In line with the Code, Lilly had updated its standard operating procedures (SOPs) and now medically approved all meetings organised for or attended by journalists to ensure that they complied with Clause 19; furthermore all such meetings were certified, if held outside the UK. In future, and where appropriate, consumer journalists would be invited to attend only Lilly certified meetings.

The unapproved articles written by the journalist fell outside the controls set by Lilly's SOPs but the company considered that its more robust approval process would prevent the likelihood of a similar circumstance arising. Lilly regretted that this very unfortunate incident occurred and reiterated its commitment to adhere to both the spirit and tenets of the Code.

Lilly explained that during November 2005 its public relations (PR) agency verbally invited the journalist, at Lilly's request, to attend the ESSM and provided her with a proposed itinerary. No material (including the symposium booklet) or press pack was provided to the journalist in connection with her sponsorship or attendance at the conference by Lilly UK or its overseas affiliates. Neither Lilly nor its agency gave the journalist a packshot of Cialis. It was Lilly's standard practice not to give consumer journalists pack shots of any of its medicines.

The patient featured in one of the articles was not known to Lilly or its PR agency. The patient details and statements by the doctor referred to in the articles were not made available to journalists at the conference. The journalist interviewed the doctor at the conference. The meeting was set up by Lilly, at the journalist's request, and was run by the journalist. The doctor was not briefed or paid by Lilly for the interview.

Some time after the conference, the doctor informed Lilly that the journalist had asked him some follow-up questions to the interview conducted at the ESSM. Lilly had not arranged or facilitated this further contact. The journalist told the doctor that she was writing articles about ED and he was concerned about her line of questioning which involved the connection between consumption of alcohol and erectile dysfunction. Lilly advised the doctor on how to handle such questions.

Lilly noted, however, that although there was one reference to Cialis and Viagra in the journalist's questions to the doctor, this question related to prevalence of ED and that the journalist told the doctor that she was writing articles on ED. The assistance offered to the doctor by Lilly concentrated on how to effectively deal with questions from the media and did not pertain to Cialis. Lilly did not believe or suspect that the articles were anything other than general disease articles, specifically because the journalist told the doctor that she was writing articles about ED and her questions to him related to ED in general. Moreover, in helping the doctor respond to the journalist's questions, Lilly did not refer to Cialis or include any Cialis messages but suggested responses relevant to the disease.

In respect of Clause 20.1 of the Code, Lilly accepted that it would have been good practice (although not stipulated by the Code) to tell the journalist about the provisions of the Code and to request that any articles that she might have wanted to write in the consumer press should either have been about ED as a disease (and not specifically about any treatment), or only have been allowed if approved by Lilly. Lilly furthermore accepted that arrangements for the journalist's attendance at ESSM should have been more closely controlled so that she understood Lilly's commitments under the Code. Lilly therefore accepted that it had failed to ensure that prescription only medicines were not advertised to the general public.

In respect of Clause 20.2 of the Code, Lilly did not accept that any of its actions in respect of the journalist's attendance at ESSM contravened this clause, as the information presented to the public was in the journalist's control and Lilly did not request, mandate or pay her for either article, nor did Lilly approve either article. Lilly, in helping the doctor to respond to the journalist's questions, clearly concentrated on ED as a disease and did not directly or indirectly provide the journalist with information on Cialis that could be interpreted as factually incorrect or unbalanced or as raising unfounded hopes or as statements that would encourage the public to ask for a specific medicine. The Code allowed information on diseases and non-promotional information on prescription only medicines to be provided to the general public and this was what Lilly anticipated it was doing when it helped the doctor to respond to the journalist's questions. Lilly could only be responsible for the information actually (directly or indirectly) provided to the journalist (ie at ESSM, which was a medical meeting of high standing, and in helping the doctor to respond to the journalist's questions, which all related to ED as a disease) and should not be held responsible for the actual content of the published articles.

In respect of Clause 2 of the Code, Lilly did not accept that any of its actions in respect of the journalist's attendance at ESSM contravened this clause. A ruling

of a breach of Clause 2 of the Code should be reserved for cases which required a sign of particular censure and Lilly believed that its actions in this case should not attract such censure. Lilly had supported the journalist (by way of travel and accommodation sponsorship) to attend ESSM. Lilly did not request, mandate or pay the journalist to write either article and had not approved their content. Once Lilly knew about these articles it asked the journalist not to write further articles about Cialis based on the information gathered due to her presence at ESSM. Prior to the articles being printed Lilly was under the impression that the journalist would be writing articles on ED, ie the disease of ED, and had helped the doctor to respond to her queries with general information about ED as a disease, which was acceptable under the Code. As a result of these articles being published, Lilly had further strengthened its SOPs to ensure that in future and where appropriate, consumer journalists would be invited to attend only Lilly certified meetings. Lilly therefore maintained that its actions had not brought discredit upon or reduced confidence in the pharmaceutical industry.

PANEL RULING

The Panel noted that the articles entitled 'Not tonight, darling' (Take a Break magazine) and 'New techniques in medicine. A new lease of love life for men' (Choice magazine) discussed ED, its causes and treatment. The article in Take a Break focussed on the condition in younger men, the other featured a more detailed discussion of ED and Cialis trial data with particular emphasis on a continuous daily dosing regime which was currently strongly discouraged as the long-term side effects after prolonged use had yet to be studied. The article in Choice magazine specifically referred to the proceedings at ESSM.

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2 permitted information to be supplied directly or indirectly to the general public but such information had to be factual and provided in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The Panel noted that Lilly had invited the journalist to and sponsored her attendance at ESSM in December 2005 and provided her with a proposed itinerary.

Whilst the itinerary described presentations about ED and general issues in sexual medicine as optional, the Lilly ICOS symposium 'ED and Beyond – Lessons to Learn from the Past for the Future' was compulsory. This included a podium session on the unlicensed dosage regimen of Cialis once daily everyday. The media interview with the doctor (who was later quoted in the two articles) was listed as a compulsory event. The Panel noted that Lilly had arranged the interview at the journalist's request although she had run the interview. Whilst the Panel noted Lilly's submission that neither it nor its affiliates or PR agency had provided any material, including a press pack to the journalist, Lilly had nonetheless made attendance at the Cialis symposium compulsory. The Panel considered that irrespective of whether Lilly had provided any material to the journalist it should nonetheless have satisfied itself that the content of the Lilly symposium was appropriate for the journalist in relation to the Code. The Panel noted that the company had amended its SOPs to ensure that all such meetings held outside the UK would be certified.

The Panel noted that the journalist had contacted the doctor she had interviewed at the conference some time later with more questions about ED. Lilly had given the doctor general media advice. The conference had taken place in December 2005 and the first of the articles in question was published in March 2006.

The Panel considered that there was no evidence that Lilly had provided any information or material to the journalist which was inconsistent with Clause 20.1 of the Code and accordingly ruled no breach of that clause. With regard to Clause 20.2 of the Code, the Panel noted that Lilly had arranged for the journalist to attend a clinical symposium at which Cialis would be discussed; there was particular focus on the use of continuous once daily treatment. The article in Choice magazine had specifically referred to proceedings at ESSM. The Panel could not understand why Lilly had arranged for the journalist's attendance at ESSM, insisted that she attend the company sponsored symposium and then asked her not to write about it. On balance the Panel considered that Lilly had provided the journalist with information that would encourage patients to ask their doctor to prescribe Cialis. A breach of Clause 20.2 of the Code was ruled.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used to indicate particular censure and was reserved for such circumstances.

Proceedings commenced **21 September 2006**

Case completed **21 November 2006**

CASE AUTH/1892/9/06

MEMBER OF THE PUBLIC v PROSTRAKAN

Rectogesic press release

A member of the public complained about the following statement in a press release issued by ProStrakan announcing the outright purchase of worldwide rights to, *inter alia*, Rectogesic (glyceryl trinitrate (GTN) rectal ointment):

> **'Rectogesic is a 0.4% topical nitroglycerin ointment indicated for the treatment of pain associated with chronic anal fissures. It is the only prescription medicine licensed specifically for the relief of this condition.**
>
> **Rectogesic works by relaxing the vascular smooth muscle around the anal canal leading to the dilation of peripheral arteries and veins, aiding the healing of the fissure. It is estimated that at any one time up to 800,000 individuals suffer from anal fissures in the EU.'**

The complainant noted that Rectogesic was not indicated for the healing of anal fissures; it was indicated for pain relief in chronic anal fissures. The statement referred to the licensed indication for Rectogesic but the second paragraph implied efficacy for the product which it did not possess and which was outside its licence. A breach of the Code was alleged.

The Panel noted that the main part of the press release stated the indication for Rectogesic ie the treatment of pain associated with chronic anal fissure. The statement at issue relating to the healing of anal fissures, was at the end of the press release in the 'Notes to Editors'.

The Panel noted that Section 5.1 of the summary of product characteristics (SPC) gave a pharmacodynamic explanation as to why GTN ointment might heal fissures, but nonetheless Rectogesic was not so licensed. The Panel considered that the statement that Rectogesic aided 'the healing of fissures' was inconsistent with the particulars listed in the SPC and thus inaccurate in that regard; high standards had not been maintained. Breaches of the Code were ruled. As the press release consisted mainly of financial information and did not promote Rectogesic *per se* and therefore did not promote an unlicensed indication the Panel ruled no breach of the Code and this was upheld on appeal by the complainant.

The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure. This ruling was upheld on appeal by the complainant.

A member of the public complained about a press release issued by ProStrakan Group Plc announcing the outright purchase of worldwide rights to, *inter alia*, Rectogesic (glyceryl trinitrate (GTN) rectal ointment).

COMPLAINT

The complainant noted that an earlier complaint, Case AUTH/1826/4/06, had not been upheld. He had been concerned that in a newspaper article ProStrakan was seeking to promote Rectogesic for unlicensed indications such as healing of anal fissures, or pain relief in acute fissures, whereas it was only indicated for pain relief, and then only in chronic anal fissures. A breach of Clause 3.2 had been alleged. In its ruling the Panel had noted that: 'The statement that Rectogesic was an ointment for the treatment of anal fissures was not in quotation marks in the article but was attributed to ProStrakan. The article was misleading in this regard but the Panel did not consider this was the responsibility of ProStrakan. In the absence of any detail of what ProStrakan said to the journalist no breach of the Code was ruled'. The complainant understood this ruling to mean that the Panel agreed with him that the article was misleading but that there was insufficient evidence to support the contention that ProStrakan had conveyed this false impression.

The complainant noted that a press release issued by ProStrakan on 27 September (www.ProStrakan.com/latest_351.php) which dealt with the proposed acquisition by ProStrakan of the global rights to Rectogesic from an American company called Cellegy, contained the following:

> 'Rectogesic is a 0.4% topical nitroglycerin ointment indicated for the treatment of pain associated with chronic anal fissures. It is the only prescription medicine licensed specifically for the relief of this condition.
>
> Rectogesic works by relaxing the vascular smooth muscle around the anal canal leading to the dilation of peripheral arteries and veins, aiding the healing of the fissure. It is estimated that at any one time up to 800,000 individuals suffer from anal fissures in the EU.'

The complainant alleged that the press release was in breach of Clause 3.2 because Rectogesic was not indicated for the healing of anal fissures. On this occasion the company could not deny responsibility. The statement did refer to the licensed indication for Rectogesic but the second paragraph implied efficacy for the product which it did not possess and which was outside its licence ie healing. This was confirmed by reference to the Scottish Medicines Consortium (SMC) report on its rejection of Rectogesic. According to the complainant the report stated: 'The company provided details of two unpublished dose-finding trials, the results from which were provided in confidence. The first dose-finding study was principally designed to assess healing rates, which is outside the product licence'.

The complainant also noted there was no mention anywhere in the Rectogesic summary of product characteristics (SPC) of its use as a treatment to aid the healing of anal fissures. Section 5.1 discussed the effects on relaxation of the anal sphincter and improvements in blood flow but there was no mention of healing.

In addition to Clause 3.2 cited by the complainant, the Authority also asked the company to respond in relation to the requirements of Clauses 2, 9.1 and 20.2 of the Code.

RESPONSE

ProStrakan explained that the press release had been distributed to the Stock Exchange and posted on the company website; as a publicly listed company ProStrakan was legally bound to inform its shareholders of price sensitive information. The company knew that prescription only medicines should not be advertised to the public, as could be seen from the nature, tone and content of the press release it was providing information to institutions and shareholders. ProStrakan appreciated the press release was in the public domain and as such the information contained within was balanced, factual and non-promotional, therefore, it did not seem appropriate for this to be dealt with under Clause 3.2 of the Code.

ProStrakan stated that the indications for Rectogesic were clearly stated in the second paragraph of the main text ('Rectogesic was launched in the UK in May 2005 as the only prescription only product approved for the treatment of pain associated with chronic anal fissure.') and repeated in the 'Notes to Editors' ('Rectogesic is 0.4% topical nitroglycerin ointment indicated for the treatment of pain associated with chronic anal fissures. It is the only prescription medicine licensed specifically for the relief of this condition.') as noted by the complainant.

The press release clearly identified the business importance of the information, it did not encourage members of the public to ask for a prescription and was non-promotional.

The detail of the mode of action of Rectogesic outlined within the 'Notes to Editors', explained a well-accepted principle of GTN action. Schouten *et al* (1994) was the first to demonstrate the ischaemic nature of chronic anal fissures. The publication of the landmark study by Lund *et al* (1997) demonstrated that as a nitric oxide donor GTN caused reversible relaxation of the anal sphincter improving anodermal blood flow and improving the environment for healing. ProStrakan provided a letter from Lund written to the SMC as part of a package of data and evidence for its consideration. This provided a very clear summary of the current situation with respect to Rectogesic in clinical practice, which was reinforced by a recently published treatment algorithm (Lund *et al* 2006).

ProStrakan submitted that the press release was of significant business importance and was non-promotional, with the indication for Rectogesic clearly stated twice. The mode of action of Rectogesic was simply explained in the 'Notes to Editors' as chronic anal fissures was a very uncommon problem. This information was presented in an open, balanced and fair way, with no implication of 'off licence' use as this was a non-promotional communication. ProStrakan did not consider that the press release breached Clause 3.2 of the Code or Clauses 2, 9.1 and 20.2.

PANEL RULING

The Panel noted that the press release announced the outright purchase of worldwide rights to, *inter alia*, Rectogesic. The body of the piece stated that Rectogesic was launched in the UK in May 2005 as the only prescription product approved for the treatment of pain associated with chronic anal fissures. In a section at the end of the press release, headed 'Notes to Editors', it was stated that Rectogesic was indicated for the treatment of pain associated with chronic anal fissures and that the product worked by relaxing vascular smooth muscle around the anal canal leading to the dilation of peripheral arteries and veins, aiding the healing of the fissure.

The Panel noted that the Rectogesic SPC stated that the therapeutic indication was 'relief of pain associated with chronic anal fissure'. Section 5.1 of the SPC, pharmacodynamic properties, noted that a link between internal anal sphincter hypertonicity and spasm and the presence of anal fissure had been established. In patients whose fissures healed following sphincterotomy a reduction in anal pressure and improvement in anodermal blood flow was demonstrated. Topical application of GTN relaxed the anal sphincter, resulting in a reduction in anal pressure and an improvement in anodermal blood flow. Notwithstanding this pharmacodynamic explanation as to why GTN ointment might heal fissures, Rectogesic was not so licensed; it was only licensed for the relief of pain. In that regard the Panel considered that the statement that Rectogesic aided 'the healing of fissures' was inconsistent with the particulars listed in the SPC and thus inaccurate in that regard. A breach of Clause 20.2 was ruled. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel ruled no breach of Clause 3.2 as the press release consisted mainly of financial information and did not promote Rectogesic *per se* and therefore did not promote an unlicensed indication. This ruling was appealed.

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

APPEAL BY COMPLAINANT

The complainant disagreed with ProStrakan's contention, and the Panel's ruling that the press release did not constitute promotion. ProStrakan had stated that the nature, tone and content of the press release demonstrated that it had provided information to institutions and shareholders. The Panel noted in its ruling that the press release consisted mainly of financial information and did not promote Rectogesic *per se* and therefore did not promote an unlicenced indication. However, the complainant noted that on the homepage of the ProStrakan website (www.ProStrakan.com) there was a prominent box headed 'Latest Developments' (please note that it was not headed 'Latest *Financial* Developments') within which was scrolling text which advertised the company's latest press releases. Press releases of all types were posted in this box, including the one at issue. At the top of the home page was a list of sections within the website including one entitled 'Investor Relations' which contained lots of financial information about the company. It also contained a menu on the left hand side of the page which included 'press releases'. Thus, if, as ProStrakan had

stated, posting this press release in this way on its website was because it was legally bound to inform its shareholders of price sensitive information, why did it not just post it in the press release section of its 'Investor Relations' section of its website? Surely this was a much more targeted and specific means of informing investors about financial events. ProStrakan might argue that posting the press release on the front page where everyone could see it was a more certain way of drawing the attention of shareholders to this important financial information. So then why did ProStrakan not advertise all of its financial press releases on the front page of its website? For example, the press releases posted on the 'Investor Relations' section of the website included one which dealt with share options recently issued to directors and managers of the company and was presumably also released for the purpose of providing information to institutions and shareholders ('ProStrakan Group plc Share Plans', 13 October 2006). Why was one of these press releases posted prominently on the home page of the company's website and the other not. The complainant alleged that it was because the press release at issue was being used to advertise prescription products. If this was the case and if, as already agreed, the document did not accurately reflect the licensed indication, then surely this constituted a breach of Clause 3.2. Therefore the complainant appealed the Panel's ruling of no breach of Clause 3.2.

The complainant noted Clause 2 and on reading ProStrakan's response had become increasingly concerned about the company's behaviour. ProStrakan had stated that the paper 'An evidence-based treatment algorithm for anal fissure' (Lund *et al* 2006) reinforced the current situation with respect to Rectogesic. The complainant found this to be an interesting description of a document which discussed unlicensed applications of topical nitrates. For example:

Page 2, paragraph 2: 'When used in the treatment of patients with chronic anal fissure, topical nitrates lead to healing in approximately two-thirds of patients'

Page 2, paragraph 5: 'Little is reported about recurrence rates after healing with nitrates'

Page 3, paragraph 2: 'On diagnosis of anal fissure, first line treatment with topical nitrates or calcium channel blockers should begin'. Rectogesic was only indicated for the relief of pain associated with chronic anal fissures.

Page 3, paragraph 3: 'Those unhealed but asymptomatic or with notable symptomatic improvement may be offered a further 6-8 weeks of topical therapy'. Rectogesic was not indicated for patients without pain.

Page 2, paragraph 3 : 'Most studies of GTN have used 0.2% ointment. Dose finding studies have now found that a 0.4% concentration may be more effective and it is this concentration which is used in commercially available GTN ointment'. Rectogesic contained 0.4% GTN.

That ProStrakan should use this document to defend its advertising of an unlicensed use of Rectogesic was frankly astonishing. However, the astonishment was tempered somewhat by the end of the document which stated: 'Acknowledgments: Supported by an educational grant from ProStrakan'. The complainant did not know what was meant by an 'educational grant' but in light of ProStrakan's involvement in this publication and its extensive discussion of uses of topical nitrates for which Rectogesic was not licensed, the following questions needed to be asked:

In the final paragraph of the introduction Lund *et al* stated 'In December 2005, we met with the aim of developing an evidence-based treatment algorithm for anal fissure aimed to optimize the pharmacological treatment in primary care'. What involvement did ProStrakan have in arranging this meeting? For example:

Who chose the participants?, Where did the meeting take place?, Was ProStrakan involved in setting the agenda?, Did ProStrakan staff participate in the meeting? Did ProStrakan pay for this meeting?, Etc, etc, etc. What role did ProStrakan play in the writing of the manuscript?, Did it: pay for the manuscript to be written?, have any editorial input into its content?, review the manuscript prior to publication?, play any role in choosing the authors?, Etc, etc, etc.

Furthermore, the complainant noted that at a meeting of the European Society of Coloproctology in September 2006, ProStrakan sponsored a satellite symposium entitled 'European treatment algorithm for anal fissure'. The four speakers at this symposium (including the chairman) were all co-authors of Lund *et al*. The titles of the presentations at this symposium were: 'The evolution of non-surgical therapy'; 'The development of a licensed GTN'; 'The development of a European treatment algorithm'. Details of this meeting could be found at: www.escp.eu.com/includes/download.php?id=25.

Unlike ProStrakan the complainant did not consider that the Authority was the place to get into a discussion (with ProStrakan or its advisors) as to whether Rectogesic should be licensed for healing of anal fissures. The complainant stated that, for one thing, he had no expertise in this area! The right place to do that was with the regulatory authorities. If ProStrakan had sufficient data to get the indication licensed then it should do so. That it had failed to do so did not give it the right to either claim it anyway or to support publications which claimed it. Therefore, the complainant alleged that the cumulative effect of the above was to constitute a breach of Clause 2 and the appeal was on this basis.

COMMENTS FROM PROSTRAKAN

ProStrakan submitted that it had clearly outlined the rationale for the press release as non-promotional in nature and not in breach of Clauses 2 and 3.2, it therefore agreed with the Panel's ruling. The financially important nature of the material in relation to the company's expansion into the US was obviously significant. It was posted on the front page website and a link from the investors section where all other non share price sensitive information was located.

ProStrakan noted that in its response to the Clause 9.1 and 20.2 allegations, it had presented an overview of the published evidence regarding the treatment of chronic anal fissures in an editorially independent paper authored by leading European experts in the management of this condition (Lund *et al*). This paper was in line with all 'educational grants'. In addition to the other references previously provided ProStrakan submitted that it had provided a clear overview of the current data and management issues in this area in the context of its response to the original complaint.

FURTHER COMMENTS FROM THE COMPLAINANT

With regard to the alleged breach of Clause 3.2, the complainant noted that ProStrakan had added very little. With regard to Clause 2 the complainant noted that ProStrakan continued to contend that it had merely provided an overview of the current data, management issues and published evidence relating to anal fissures. Its overview was unbalanced, but the complainant did not possess the expertise to argue this point. However, the company's opinions about the role of Rectogesic in the healing of anal fissures, interesting though they might be, should not take precedence over the authorities responsible for licensing the medicine. Rectogesic did not have a licence for fissure healing. Furthermore, it appeared that the medicine (known as Cellegesic in the US) had been refused a licence by the US government for either healing or pain. Indeed, the press release at issue, stated:

> 'In July, the Food and Drug Administration (FDA) granted Cellegesic approvable status in the US, conditional upon a further clinical trial being successfully conducted. ProStrakan will initiate this trial as soon as practicable following closure of the acquisition. Upon successful completion of the trial, the results would be submitted to the FDA with a view to pursuing full US approval.'

The complainant referred to the FDA websites, in particular to section 1 of a 2004 FDA report on Cellegesic and the minutes of an FDA meeting to discuss the Cellegesic application which took place on 25 April 2006. Dr Lund spoke to the FDA on behalf of Cellegy at this meeting. At the conclusion of the meeting the FDA decided that Cellegesic could only be approved for the treatment of fissure pain 'pending another study of effectiveness'.

The complainant alleged that importantly, both these documents stated clearly that a company sponsored clinical study conducted specifically to determine whether this medicine had any effect on the healing of anal fissures showed clearly that it did not. Thus, these documents indicated strongly why Rectogesic did not have a licence for the healing of anal fissures and why it should not be promoted as such by ProStrakan, either overtly or indirectly.

The complainant noted the specific questions about the algorithm publication; questions which were set out in the appeal and which were not addressed by ProStrakan. The complainant hoped that these questions would be raised at the appeal.

APPEAL BOARD RULING

The Appeal Board noted that ProStrakan had accepted the Panel's rulings of breaches of Clauses 9.1 and 20.2.

The Appeal Board upheld the Panel's ruling of no breach of Clause 3.2 as the press release was not a promotional item; it consisted mainly of financial information and thus did not promote Rectogesic *per se* for an unlicensed indication. The appeal on this point was unsuccessful.

The Appeal Board did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was used as a sign of particular censure. The Appeal Board thus upheld the Panel's ruling of no breach of Clause 2. The appeal on this point was also unsuccessful.

Complaint received	**29 September 2006**
Case completed	**7 December 2006**

CASE AUTH/1894/10/06

NOVARTIS v ASTRAZENECA

Arimidex mailing

Novartis complained that an Arimidex (anastrozole) mailing issued by AstraZeneca presented an oversimplified and misleading cost comparison which failed to compare like with like in terms of the indications. The mailing featured a table comparing the 28 day cost of three aromatase inhibitors in the treatment of breast cancer: Arimidex 1mg (£65.56); letrozole 2.5mg (Novartis' product Femara) (£83.16) and exemestane 25mg (Pharmacia's product Aromasin) (£82.88).

The indications for Arimidex were:

'Treatment of advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen.

Adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer.

Adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.'

The indications for Femara were:

'Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.

Treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.

First-line treatment in postmenopausal women with advanced breast cancer.

Advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy has failed.

Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for breast-conserving surgery. Subsequent treatment after surgery should be in accordance with standard of care.'

The indications for Aromasin were:

'In patients with early breast cancer, treatment with Aromasin should continue until completion of five years of combined sequential adjuvant hormonal therapy (tamoxifen followed by Aromasin), or earlier if tumour relapse occurs.

In patients with advanced breast cancer, treatment with Aromasin should continue until tumour progression is evident.'

Given these differences Novartis alleged that it was misleading to make a cost comparison without specifying what indications were being referred to.

The Panel noted that the indications for the products differed. When Arimidex was used in accordance with its licence it would be less expensive than the other products listed when they were also so licensed. However the cost comparison appeared beneath a general heading relating to the treatment of breast cancer. Letrozole was licensed for two indications (pre-surgery treatment and following five years of tamoxifen therapy post-surgery) for which Arimidex was not. There was no information stating that the indications differed. The Panel considered that the item was a misleading comparison and a breach of the Code was ruled.

Novartis Pharmaceuticals UK Ltd complained about a cost comparison mailing (ref ARIM 06 18944) for Arimidex (anastrozole) issued by AstraZeneca UK Limited. The mailing featured a table comparing the 28 day cost of three aromatase inhibitors in the treatment of breast cancer: Arimidex 1mg (£65.56); letrozole 2.5mg (Novartis' product Femara) (£83.16) and exemestane 25mg (Pharmacia's product Aromasin) (£82.88).

COMPLAINT

Novartis alleged that the cost comparison was oversimplified and presented a misleading impression of the relative costs of the products and failed to compare like with like in terms of the indications as required by the Code. A breach of Clause 7.2 was alleged.

The licensed indications for the three products included in the cost comparison were not the same. The indications for Arimidex were:

'Treatment of advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen.

Adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer.

Adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.' (Arimidex summary of product characteristics (SPC)).

The indications for Femara were:

'Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer.

Treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy.

First-line treatment in postmenopausal women with advanced breast cancer.

Advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy has failed.

Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for

breast-conserving surgery. Subsequent treatment after surgery should be in accordance with standard of care.' (Femara SPC).

The indications for Aromasin were:

'In patients with early breast cancer, treatment with Aromasin should continue until completion of five years of combined sequential adjuvant hormonal therapy (tamoxifen followed by Aromasin), or earlier if tumour relapse occurs.

In patients with advanced breast cancer, treatment with Aromasin should continue until tumour progression is evident.' (Aromasin SPC).

The different indications were summarised in the table below.

Given the differences between the products, Novartis alleged that it was misleading to make a cost comparison without specifying what indications were being referred to. This was a misleading comparison in breach of Clause 7.2.

RESPONSE

AstraZeneca stated that the mailer in question was prepared in June 2006 and its primary purpose was to compare the acquisition costs per 28 days' treatment with anastrozole (Arimidex), letrozole or exemestane. The cost comparison was based on the June 2006 issue of MIMS. These three aromatase inhibitors were normally prescribed to prevent breast cancer recurrence.

The item was sent to hospital pharmacists and network pharmacists (the latter had responsibilities in the delivery of agreed cancer action plans for the local cancer network). Cancer action plans were based on evidence based treatment strategies and evaluation of costs. As such, cancer network pharmacists were a small, specialized group responsible for clinical and budgetary planning across a larger geographical region; currently there were 34 networks covering England; hospital trusts often looked to cancer networks to advise them on such matters.

The mailer contained two stand alone items: one about a recently acquired licensed indication for Arimidex and one about the acquisition costs of anastrozole, letrozole and exemastane. Acquisition costs were important because they allowed pharmacists to make informed decisions that impacted on drug-purchasing budgets thus optimising limited healthcare resources.

The item at issue clearly stated in the prescribing information the licensed indications for Arimidex. Both exemestane and letrozole shared common indications with Arimidex. As such the item at issue aimed to compare the cost of Arimidex with letrozole for the 'Adjuvant treatment of postmenopausal women with hormone receptor positive early invasive breast cancer' and with exemestane for the 'Adjuvant treatment of early breast cancer in hormone receptor positive postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen'. Finally all three products shared common licence indications in the advanced breast cancer setting.

AstraZeneca knew that under the Code price comparisons could only be made where like was compared with like. This requirement had been met because the dosage and dosage frequency (one tablet daily) of each product, as shown in the mailer, did not change across indications. This meant that the cost per 28 days' treatment for each product was as shown in the mailer. Furthermore, the acquisition costs for each of the three products compared over 28 days was appropriate because treatment typically lasted months to years rather than days or weeks, eg treatment of advanced breast cancer with aromatase inhibitors typically lasted for months, whereas treatment of early breast cancer would typically be for up to five years.

AstraZeneca also recognised that price comparisons should be made on the basis of the equivalent dosage requirement for the same indication. This requirement was not relevant in this case because regardless of the specific indications for each of the three products, usage rates were identical for 28 days' treatment: patients who were treated with any of the three aromatase inhibitors would have to take one tablet daily. Moreover, as no aromatase inhibitor had been shown to be superior over another in terms of efficacy, reducing treatment duration, improving patient compliance or improving adverse event profiles, the only valid price comparison was the one shown in the mailer, ie direct acquisition costs.

Therefore, AstraZeneca denied a breach of Clause 7.2 given the reasons outlined above.

PANEL RULING

The Panel noted that the material at issue sent to hospital and network pharmacists included the costs of 28 days' treatment with Arimidex (£68.56), letrozole (£83.16) and exemestane (£82.88) beneath the heading

	Pre-surgery (neoadjuvant)	*Post-surgery (adjuvant)*	*Within five years post-surgery – switching from tamoxifen (adjuvant switch)*	*Following five years of tamoxifen therapy post-surgery (extended adjuvant)*	*Advanced breast cancer*	
					First-line	*Second line*
Femara (letrozole)	✓	✓		✓	✓	✓
Arimidex (anastrozole)		✓	✓		✓	✓
Aromasin (exemestane)			✓			✓

'Comparing the cost of Aromatase Inhibitors in the treatment of breast cancer'.

The Panel noted that the indications for the products differed. When Arimidex was used in accordance with its licence it would be less expensive than the other products listed when they were also so licensed. However the cost comparison appeared beneath a general heading relating to the treatment of breast cancer and Arimidex was not the least expensive medicine for the treatment of all types of breast cancer. Letrozole was licensed for two indications (pre-surgery treatment and following five years of tamoxifen therapy post-surgery) for which Arimidex was not. There was no information stating that the indications differed. The Panel considered that the item was a misleading comparison and a breach of Clause 7.2 of the Code was ruled.

Complaint received **6 October 2006**

Case completed **29 November 2006**

CASE AUTH/1896/10/06 *NO BREACH OF THE CODE*

ANONYMOUS v LILLY

Alleged inappropriate hospitality

An anonymous complainant complained about the activities of, *inter alia*, Lilly with regard to hospitality provided to members of various national associations for asian psychiatrists working in the UK who generally grouped together to hold meetings either in the UK or abroad. The complainant drew particular attention to a meeting held at Heathrow and sponsored by Lilly at which attendees enjoyed an evening music/cultural programme at Lilly's expense. The complainant alleged that the meetings organised by the various associations were more of a social get together rather than recognized academic meetings.

The Panel noted that the Heathrow meeting started at 10am and lasted until 4.45pm followed by the annual general meetings of each of four national associations of asian psychiatrists working in the UK (India, Pakistan, Sri Lanka, Arabia). The agenda stated that Lilly had provided an unrestricted educational grant. The final agenda in relation to dinner stated 'Conference Reception, Dinner & Music Programme'.

The Panel considered that according to the draft provisional agenda, the scientific/educational content was not unreasonable for sponsorship by a pharmaceutical company. The draft agenda referred only to a 'Conference Dinner'. The prime purpose of the meeting was scientific/educational.

The Panel noted that the sponsorship from Lilly was for the day-time scientific meeting. The organisers stated that the ABPI guidelines for the meeting, which was only open to medical professionals, would be followed.

Lilly's sponsorship had covered the daily delegate rate, lunch costs, logistical costs plus a contribution to the delegate registration fee. The Panel was concerned that Lilly did not know what the latter covered; it had assumed it covered travel and honorarium costs for speakers as well as printing costs for materials used at the meeting.

The Panel was concerned that Lilly had not insisted on seeing the final programme. The final programme differed from the provisional agenda. In particular a one hour symposium shown on the draft agenda was not on the final programme. The Panel was also concerned that Lilly did not know about all the arrangements. There did not appear to be any educational programme on the Sunday. The Panel also queried whether the evening reception, dinner and entertainment were appropriate for Lilly to sponsor given that the event appeared to be more of a social event rather than subsistence provided after a meeting. However, there was no evidence that Lilly's payment of logistical costs and its contribution to the delegate registration fee had paid for or subsidised the reception, dinner and music programme. On balance the Panel considered that the sponsorship by Lilly for the meeting as described on the draft agenda was not unacceptable. No breach of the Code was ruled.

An anonymous complainant complained about the activities of a number of companies including Eli Lilly and Company Limited.

COMPLAINT

The complainant stated that in the last few years, a few psychiatrists had established a very close personal relationship with pharmaceutical companies. These psychiatrists had been using pharmaceutical companies for their personal advantages, benefits, ambitions and personal growth. They had established the South Asian Forum. They organised two or three meetings of the South Asian Forum in the UK and outside the UK, such as in India, Pakistan and Sri Lanka where Asian psychiatrists met together. All the expenses of hotel, travel and food were 'sponged' by pharmaceutical companies. Until recently a named company had 'sponged' Asian psychiatrists to travel to Pakistan in 2004, to India in January 2005, to Sri Lanka in July 2005. All these psychiatrists were friendly to each other and enjoyed these meetings as an opportunity to meet each other. They invited them to attend the meetings and money was paid by pharmaceutical companies. They maintained the database of most of the Asian and Arabic psychiatrists. It was a numbers game. They had numbers to influence the pharmaceutical companies and pharmaceutical companies tried to oblige the vulnerable psychiatrist who could increase prescriptions.

It was very important to investigate the list of participants who went to India, Sri Lanka and Pakistan. It was also important to check with the participants who invited them, who motivated them and how money was paid for their visits. Interestingly it was decided who would go or not go to the outside UK meeting by two or three psychiatrists most of the time. These few psychiatrists invited all the Asians by email, telephone and post. They might be able to provide the addresses of all the Asians and Muslim psychiatrists to pharmaceutical companies. In this kind of meeting they organised a very fascinating Asian cultural programme that was also a motivating factor to all Asians to attend this kind of meeting.

More recently (9 September 2006) these few psychiatrists played an important role to organize one grand meeting which combined the South Asian Forum and Islam Association, British Pakistan Psychiatrist Association, British Indian Psychiatrist Association and Arabic Association of Psychiatrists at the Marriott Hotel, Heathrow. The complainant believed that Lilly was involved in this meeting. All the Asians and Muslims enjoyed evening dance, music and cultural programme partly at the expense of pharmaceutical companies (Lilly).

It would be worthwhile to note that these kinds of meetings were more of a get together and based on similar cultures/religions not internally recognized academic meetings. The majority of delegates were attending again and again. There was a numbers game, this group could manage more than 100 psychiatrists to attend the meeting and it influenced the pharmaceutical companies to breach the Code. This numbers game and desire of a few psychiatrists for using pharmaceutical monies for their personal advantage/growth made pharmaceutical companies to become more tempted.

This South Asian Forum was a regional association and should not grow on the basis of pharmaceutical money. This association also closely worked with Islam association; about fifty percent of delegates were in common. One of the above psychiatrists had been instrumental in these two associations. These two associations would disappear within a few weeks if not days if they did not have financial support from pharmaceutical companies. It was evident that initially for two to three years one named company supported these kinds of meetings.

Motivating factors for participants:

1 Free hotel and sense of holiday; find it a nice weekend break.

2 Meeting common friends.

3 Enjoying night cultural programme.

4 In the night enjoying Asian food.

Motivating factors for organizer:

1 They tried to influence and build up relationships with world prominent psychiatrists who they invited as speakers and then used them for personal growth.

2 They reflected their strength to those who were contesting for any post in World Psychiatrist Association and got closer to them.

Motivating factor for pharmaceutical companies:

1 Take advantage of numbers and try to push their sales.

2 Need for investigation to establish whether there has been a breach of the Code.

3 Was it appropriate to use pharmaceutical companies for their personal picnic or personal association or personal cultural meetings?

4 Was it appropriate to use pharmaceutical companies for their personal growth and uniting all Asians together and reflecting the numbers and influencing the pharmaceutical companies?

5 It was a two way process, pharmaceutical companies needed the numbers and this group of doctors needed money for their personal agendas.

When writing to Lilly the Authority asked it to respond in relation to Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

Lilly stated that the British Indian Psychiatric Association (BIPA), the British Pakistani Psychiatrists Association (BPPA), the Sri Lankan Psychiatric Association (SLPA-UK) and the British Arab Psychiatric Association (BAPA) (the four associations) held a conference 'Peace, Social Integration and Psychiatry', at the Marriott Hotel, Heathrow on 9 September 2006. It was jointly hosted by the Royal College of Psychiatrists (RCPsych).

This was their second joint biennial and fifth annual general meeting, and Lilly offered to sponsor this meeting, contingent on the arrangements complying with the Code.

Lilly received a provisional programme which confirmed the scientific, educational nature of the meeting, with inaugural lectures followed by presentations on various aspects of psychiatry over the course of the day. In this regard, it should be noted that in the letter from the Chair, Steering Committee of Associations – 'A Great Partnership' it was stipulated that this meeting was an approved continual professional development (CPD) activity and that 'This important educational event provides for the CPD requirements for consultants and is suitable for their annual appraisals in this regard'.

Lilly agreed to sponsor this scientific programme to cover the day delegate rate, lunch, meeting logistics, and contributions to the delegate registration fee for 350 health professionals. The total cost of sponsorship was £31,325. Lilly provided a breakdown of those costs as provided by the conference organisers. Lilly's sponsorship was declared on the final agenda.

The agenda was set by the steering committee of the four associations. Lilly understood that the delegates were invited by the steering committee. Lilly understood that the meeting was restricted to health professionals, and that spouses/families were not

registered for the meeting. No Lilly employees attended. Lilly was not directly or indirectly involved in setting the agenda or inviting the delegates.

Lilly had no knowledge of the music/cultural programme referred to in the final agenda. Indeed, in the draft programme received by Lilly, the meeting was followed by a 'conference dinner' at 7.30pm. Furthermore, Lilly's sponsorship of this meeting was only for the scientific programme during the day and did not extend to any of the evening activities.

Regarding the forthcoming meeting in Dubai, Lilly had been approached for sponsorship by the Chair of the South Asian Forum, UK Chapter; the request had been denied.

The meeting held on 9 September was an independent meeting organized by the four associations and the RCPysch with clear educational content. Lilly's sponsorship of this meeting pertained only to the day-time scientific programme, and subsistence in the form of lunch. Lilly therefore did not consider that it had breached Clause 19.1 of the Code. Consequently, it must follow that Lilly had also not breached Clauses 9.1 or 2.

In response to a request for further information Lilly noted that it had contributed £10,500 to delegate registration fees and was asked what this was spent on, given that Lilly had already paid the day delegate rate, lunch and room hire etc. Lilly stated that it had not asked the organisers of the meeting, to whom the educational grant was made, to specify what Lilly's portion of the contribution of the delegate registration fees was used for. Lilly however anticipated that this contribution would have been used towards paying speakers' honoraria and travel costs and printing costs associated with any materials produced in respect of this meeting.

Asked how it ensured that the £31,525 provided was spent in accordance with the Code, Lilly stated that it provided an educational grant to members of the health profession in the UK to support an educational meeting, which was jointly hosted by 'A Great Partnership' and the RCPsych. This meeting had been held before, was of high educational content and sufficiently robust in content to comply with CPD requirements for consultants. Lilly sponsored 350 psychiatrists from across the UK to attend this meeting. Lilly had confirmation in writing that ABPI guidelines for this meeting would be strictly observed and the meeting was approved through Lilly's internal 'Independent Meeting Proactive Sponsorship Proposal' standard operating procedure.

In Lilly's view these steps showed proper due diligence and, trusting on the bona fides of the health professionals who requested the sponsorship and confirmed in writing that ABPI guidelines would be strictly observed, failed to see that any further steps were necessary to ensure Code compliance. Furthermore Lilly's sponsorship of the event was duly declared at the event.

Asked why it did not see the final agenda, Lilly stated that the meeting was dependent on receiving sponsorship, which was requested in June 2006. As the meeting was dependent on the sponsorship it was impossible to finalise the agenda before the organising committee had confirmation that the sponsorship would be forthcoming. It was therefore standard practice to consider a provisional agenda to determine the educational content of a meeting and whether the sponsorship thereof would be appropriate and comply with the Code. In this case the educational content was further supported by the fact that Lilly was assured that the meeting was jointly hosted between the organisers and the RCPsych and also that the educational content met CPD requirements for consultants. Having taken the provisional agenda, the aforesaid fact in respect of the educational content of this meeting, confirmation that Lilly's sponsorship would be declared and the organisers' assurance that ABPI guidelines would be strictly observed into account, Lilly did not deem it necessary to make its sponsorship dependent on receipt of the final agenda. Often speakers and the precise topic of their talk could only be confirmed once sponsorship had been provided and dates confirmed.

In response to a request for a timetable of events starting with the initial approach for funding and including the dates when draft and final agendas were available, Lilly stated that this was the second joint bi-annual and fifth annual general meeting of 'A Great Partnership'. Lilly was aware that this meeting had taken place in the past and that it was of a high scientific quality. Lilly therefore approached the Chair, Steering Committee Associations – 'A Great Partnership' in April 2006 to discuss potential sponsorship of this event and as a result of these discussions received a proposal in respect of this meeting at the beginning of June 2006, requesting sponsorship. It was then put through Lilly's approval process in the middle of June 2006, after being formally requested on 16 June 2006. The meeting was held on Saturday, 9 September 2006 at the Marriott Hotel. The draft agenda was attached to the letter requesting sponsorship. Lilly did not receive a final agenda until receipt of the Authority's letter of 10 October 2006.

Lilly reiterated that the meeting was an independent meeting organized by the four associations and the RCPysch with clear educational content. Lilly's sponsorship of this meeting (which was declared) pertained only to the day-time scientific programme, and subsistence in the form of lunch. The meeting organisers confirmed in writing that ABPI guidelines would be strictly observed. Lilly therefore absolutely did not believe that it had breached any of the provisions of the Code in respect of its sponsorship of this independent meeting.

PANEL RULING

The Panel noted that the meeting on 9 September started at 10:00 and finished at 16:45 followed by the annual general meetings of each of the four associations until 17:45. The agenda stated that Lilly had provided an unrestricted educational grant. The final agenda in relation to dinner, stated 'Conference Reception, Dinner & Music Programme'.

The Panel considered that according to the draft provisional agenda, the scientific/educational content

was not unreasonable for sponsorship by a pharmaceutical company. The draft agenda referred only to a 'Conference Dinner'. The prime purpose of the meeting was scientific/educational.

The Panel noted that the sponsorship from Lilly was for the day-time scientific meeting. The organisers stated that the ABPI guidelines for the meeting, which was only open to medical professionals, would be followed. The sponsorship was based on 350 psychiatrists attending, the previous meeting was attended by 446 psychiatrists.

The Panel noted that Lilly had sponsored the meeting by paying the daily delegate rate, lunch costs, audio visual media and room hire plus a contribution to the delegate registration fee. The Panel was concerned that Lilly did not know what the latter covered; it had assumed it covered travel and honorarium costs for speakers as well as printing costs for materials used at the meeting.

The Panel was concerned that Lilly had not insisted on seeing the final programme as part of the sponsorship arrangements. The final programme differed from the provisional agenda with regard to the afternoon scientific session. In particular a one hour symposium (18:00-19:00) shown on the draft agenda was not on the final programme. The Panel was also concerned that Lilly did not know about all the arrangements. There did not appear to be any educational programme on the Sunday. The Panel also queried whether the evening reception, dinner and entertainment were appropriate for Lilly to sponsor given that the event appeared to be more of a social event rather than subsistence provided after a meeting. However, there was no evidence that Lilly's payment of logistical costs and its contribution to the delegate registration fee had paid for or subsidised the reception, dinner and music programme. On balance the Panel considered that the sponsorship by Lilly for the meeting as described on the draft agenda was not unacceptable and did not breach Clause 19.1 of the Code and thus no breach was ruled.

The Panel did not consider that there had been breaches of Clauses 2 and 9.1 of the Code.

Complaint received **9 October 2006**

Case completed **28 November 2006**

ANONYMOUS v JANSSEN-CILAG

Alleged inappropriate hospitality

An anonymous complainant complained about the activities of, *inter alia*, Janssen-Cilag with regard to hospitality provided to members of various national associations for Asian psychiatrists working in the UK who generally grouped together to hold meetings either in the UK or abroad. The complainant drew particular attention to a meeting held in Dubai, December 2006, sponsored by Janssen-Cilag and organised by the South Asian Forum.

The Panel noted that Janssen-Cilag had not sponsored the meeting but had sponsored 14 doctors to attend by paying for their flights, accommodation, registration fees and day delegate rate. The Panel considered that the meeting was an educational/scientific meeting. The meeting was held in association with the World Psychiatric Association and many of the speakers were from Asia or North America. In the circumstances the Panel did not think the arrangements for sponsoring UK health professionals to attend was unreasonable. No breach of the Code was ruled.

An anonymous complainant complained about the activities of a number of companies, including Janssen-Cilag Ltd.

COMPLAINT

The complainant stated that in the last few years, a few psychiatrists had established a very close personal relationship with pharmaceutical companies. These psychiatrists had been using pharmaceutical companies for their personal advantages, benefits, ambitions and personal growth. They had established the South Asian Forum. They organised two or three meetings of the South Asian Forum in the UK and outside the UK, such as in India, Pakistan and Sri Lanka where Asian psychiatrists met together. All the expenses of hotel, travel and food were 'sponged' by pharmaceutical companies. Until recently a named company had 'sponged' Asian psychiatrists to travel to Pakistan in 2004, to India in January 2005, to Sri Lanka in July 2005. All these psychiatrists were friendly to each other and enjoyed these meetings as an opportunity to meet each other. They invited them to attend the meetings and money was paid by pharmaceutical companies. They maintained the database of most of the Asian and Arabic psychiatrists. It was a numbers game. They had numbers to influence the pharmaceutical companies and pharmaceutical companies tried to oblige the vulnerable psychiatrist who could increase prescriptions.

It was very important to investigate the list of participants who went to India, Sri Lanka and Pakistan. It was also important to check with the participants who invited them, who motivated them and how money was paid for their visits. Interestingly it was decided who would go or not go to the outside UK meeting by two or three psychiatrists most of the time. These few psychiatrists invited all the Asians by email, telephone and post. They might be able to provide the addresses of all the Asians and Muslim psychiatrists to pharmaceutical companies. In this kind of meeting they organised a very fascinating Asian cultural programme that was also a motivating factor to all Asians to attend this kind of meeting.

It would be worthwhile to note that these kinds of meetings were more of a get together and based on similar cultures/religions not internally recognized academic meetings. The majority of delegates were attending again and again. There was a numbers game, this group could manage more than 100 psychiatrists to attend the meeting and it influenced the pharmaceutical companies to breach the Code. This numbers game and desire of a few psychiatrists for using pharmaceutical monies for their personal advantage/growth made pharmaceutical companies to become more tempted.

In December 2006 a South Asian Forum meeting in Dubai was being organised. Janssen-Cilag was believed to be one of the sponsor pharmaceutical companies. It was worthwhile doing undercover work during this meeting to expose the nexus between Asian psychiatrist and pharmaceutical companies.

This South Asian Forum was a regional association and should not grow on the basis of pharmaceutical money. This association also closely worked with Islam association; about fifty percent of delegates were in common. One of the above psychiatrists had been instrumental in these two associations. These two associations would disappear within a few weeks if not days if they did not have financial support from pharmaceutical companies. It was evident that initially for two to three years one named company supported these kinds of meetings.

Motivating factors for participants:

1 Free hotel and sense of holiday; find it a nice weekend break.

2 Meeting common friends.

3 Enjoying night cultural programme.

4 In the night enjoying Asian food.

Motivating factors for organizer:

1 They tried to influence and build up relationships with world prominent psychiatrists who they invited as speakers and then used them for personal growth.

2 They reflected their strength to those who were contesting for any post in World Psychiatrist Association and got closer to them.

Motivating factor for pharmaceutical companies:

1 Take advantage of numbers and try to push their sales.

2 Need for investigation to establish whether there

has been a breach of the Code.

3 Was it appropriate to use pharmaceutical companies for their personal picnic or personal association or personal cultural meetings?

4 Was it appropriate to use pharmaceutical companies for their personal growth and uniting all Asians together and reflecting the numbers and influencing the pharmaceutical companies?

5 It was a two way process, pharmaceutical companies needed the numbers and this group of doctors needed money for their personal agendas.

When writing to Janssen-Cilag the Authority asked it to respond in relation to Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

Janssen-Cilag noted that it had been asked to respond in relation to a December 2006 meeting in Dubai organised by the South Asian Forum.

Janssen-Cilag denied any breach of Clauses 2, 9.1 or 19.1. The South Asian Forum was an international organisation of consultant psychiatrists which organised international academic meetings for the psychiatric profession. The aim of the organisation was to further the improvement of psychiatry in South Asia and the rest of the world.

The forum meetings were scientific in nature, held on an annual basis and, on this occasion, the meeting was due to be held in Dubai from 2 to 6 December 2006.

Janssen-Cilag was not a sponsor of this meeting; however it had provided individual doctors with educational grants to enable them to attend. Janssen-Cilag explained that individual doctors had approached the company for sponsorship to attend this meeting, and although contacts were predominantly made through local representatives, these requests were forwarded to the medical department for assessment as to their merit.

The agenda for the meeting (copy provided) was deemed to be of sufficient scientific interest to merit support. Janssen-Cilag noted that the meeting in Dubai was held in association with the World Psychiatric Association thereby giving it further credibility.

Once the meeting was accepted as being of a sufficient standard to merit support, doctors, who had individually contacted Janssen-Cilag and which it was able to support, were provided with educational grants to cover economy air travel (£450), registration (£200), hotel (£600) and subsistence (£250). Support was provided upon the explicit understanding that it covered the period from 2 to 6 December 2006, ie the dates during which the conference was held.

In summary, Janssen-Cilag had provided educational grants to support the attendance of a number of health professionals at an international meeting with a scientific content relevant to their practice of medicine. Janssen-Cilag had not sponsored the conference, and did not consider the overall individual cost, paid to the South Asian Forum which was arranging the logistics for those health professionals attending, to be excessive, and consequently Janssen-Cilag denied breaches of Clauses 2, 9.1 and 19.1.

In response to a request for further information Janssen-Cilag noted that it had provided fourteen grants each of £1,500 (£21,000) to allow delegates to attend the meeting in Dubai. With regard to ensuring that such sponsorship was spent in accordance with the Code, Janssen-Cilag provided a copy of the standard letter it had sent to the South Asian Forum in respect of each doctor it had supported. The letter made it clear that the educational grant was for the sole use of a named consultant psychiatrist and specified that the grant covered a return economy travel, accommodation for the duration of the meeting and full registration again for that specific doctor for the given dates 2 to 6 December 2006.

A letter from the Chairman of the South Asian Forum to Janssen-Cilag confirmed that the educational grants were for individually named doctors, gave a breakdown of costs and acknowledged the terms and conditions for the provision of the education grants.

The Chairman of the South Asian Forum, also confirmed that it would provide a reconciliation of spend versus funding from Janssen-Cilag for each individual doctor following the meeting.

Janssen-Cilag provided details of each doctor's travel plans to show departure and return dates to the UK. These showed outward flights on 1 December and return flights on 6 December.

Janssen-Cilag reiterated that it believed its support of the named delegates to attend this meeting complied with the Code and that the meeting was of sufficient international and scientific stature to merit its support; hence again, it denied any breaches of Clause 2, 9.1 or 19.1 of the Code.

PANEL RULING

The Panel noted that Janssen-Cilag had not sponsored the meeting; it had sponsored 14 doctors to attend. The sponsorship had been given to the UK Chapter of the South Asian Forum.

The Panel considered that the meeting was an educational/scientific meeting which included a pre-conference symposium on 2 December from 14:00 until 16:20 with another 3½ days of educational programme.

The sponsorship provided by Janssen-Cilag related to flights arranged by the company to arrive in time for the start of the meeting and returning the day the meeting finished. The company had also paid for accommodation, the day delegate rate and conference registration fees. The meeting was held in association with the World Psychiatric Association and, according to the programme, many of the speakers were from Asia or North America.

In the circumstances the Panel did not think the arrangements for sponsoring UK health professional to attend were unreasonable. Thus the Panel ruled no breach of Clauses 2, 9.1 and 19.1 of the Code.

Complaint received **9 October 2006**

Case completed **28 November 2006**

GENERAL PRACTITIONERS v PROCTER & GAMBLE

'Dear Doctor' letter about mesalazine

Two general practitioners complained separately about a letter received from a university hospital professor, which referred to the prescribing of mesalazine preparations. The letter had been sponsored by an educational grant from Procter & Gamble. Procter & Gamble supplied Asacol (mesalazine modified release).

In both cases the complainants alleged that the letter was disguised promotion. In Case AUTH/1898/10/06 the complainant submitted that the disguise had been effected by using the professor to write the letter on his departmental letter heading (whether ghost written/edited or not), and by not mentioning the product name, when recipients would be fully aware of what was intended. The complainant further noted that letter appeared to have been sent to all UK GPs but the professor worked in a centre of excellence in another area; the complainant was very unlikely to refer patients to him. The complainant in Case AUTH/1900/10/06 submitted that the professor had completely denied responsibility for the use of the letter in a nationwide campaign.

The Panel noted that the letter was about the general issue of prescribing oral mesalazine. Recipients were reminded that mesalazine preparations differed in their release characteristics and as such should not be considered interchangeable. Once a patient was maintained on one particular brand of mesalazine it was important that they remained on that brand and were not given generic prescriptions which would mean that they might receive a different brand. The Panel noted that the letter did not mention any particular brand of oral mesalazine either by name or by implication. In that regard, given the general nature of the letter, the Panel did not consider that it promoted Asacol. The letter thus did not require prescribing information for Asacol. No breach of the Code was ruled. The letter also, therefore, did not constitute disguised promotion for Asacol. No breach of the Code was ruled.

With regard to the distribution of the letter the Panel noted that the professor had relied upon the supplier assigned to carry out the mailing. The Panel considered that if this supplier had been appointed by Procter & Gamble the company should have briefed the supplier such that there was no misunderstanding as to whom the mailing was to be sent. It was not clear who generated the final mailing list and on what basis but it appeared that the mailing had gone to more people than the professor had originally envisaged. In that regard the Panel considered that Procter & Gamble might not have managed the project with enough care to ensure that high standards were maintained. In addition the Panel noted that Procter & Gamble had paid for the mailing costs and thus the statement that the letter had been sponsored by an educational grant was misleading. In the Panel's view it was beholden upon companies not only to declare their sponsorship of material but also to be very clear about the nature of the sponsorship. Overall high standards had not been maintained. A breach of the Code was ruled.

Two general practitioners (Case AUTH/1898/10/06 and Case AUTH/1900/10/06), complained separately about a letter received from a university hospital professor, which referred to the prescribing of mesalazine preparations. The letter was dated 2 October 2006 but at the bottom of the second (and final) page it was stated that its date of preparation was 1 September 2006 and the reference AS 7285 was given. It was stated on both pages that the letter had been sponsored by an educational grant from Procter & Gamble Pharmaceuticals.

The complaints were taken up with Procter & Gamble Pharmaceuticals UK Limited, which supplied Asacol (mesalazine modified release).

Case AUTH/1898/10/06

COMPLAINT

The complainant alleged that the letter he had received from the professor was in breach of the Code as it was disguised promotion for Asacol. The disguise had been effected by the use of the professor to write it on his departmental letter heading (whether ghost written/edited or not), and by the specific device of not mentioning the product name, when recipients would be fully aware of what was intended. This dovetailed into existing overt advertising on this theme by Procter & Gamble.

The letter came to the complainant on the professor's own departmental headed notepaper as his own opinion, as it might well be. The small print at the bottom of the page indicated that it was 'Supported by an educational grant from Procter & Gamble Pharmaceuticals'. The final line 'Date of preparation 1 September 2006. AS7285' suggested AS for Asacol and 7285 being a large number had probably originated from Procter & Gamble rather than the professor. The professor had not declared the extent of this 'support' or indeed the extent to which Procter & Gamble might fund his other activities.

The letter appeared to be one of a mass mailing, presumably to all UK GPs, which was a not inconsiderable expense. The complainant did not object to the sentiment expressed, which he had long adopted, in fact, in favour of this product. This information was therefore not relevant to him. The professor might work in a centre of excellence, but it was in a different country even from the one in which the complainant worked. He had no professional relation with him and his primary care organisation would not fund NHS referrals to him except on a special and case-by-case basis.

To the complainant this was clearly a promotional mailing by Procter & Gamble to all GPs and should have been presented as such, with a quotation from the professor placed within the body of the text if appropriate.

Openness of intent and declaration of financial support was now an important part of relations between doctors and the pharmaceutical industry. The complainant would be glad if the Authority could consider this issue and communicate its findings to all parties.

Case AUTH/1900/10/06

COMPLAINT

The complainant alleged that the letter in question was disguised promotion in breach of the Code.

He had discussed the matter with the professor who completely denied responsibility for the use of this letter in a nationwide campaign.

* * * * *

When writing to Procter & Gamble about the complaints, the Authority asked it to respond in relation to Clauses 4.1 (Case AUTH/1898/10/06 only), 9.1 and 10.1 of the Code.

Cases AUTH/1898/10/06 and AUTH/1900/10/06

RESPONSE

Procter & Gamble stated that the professor had undertaken a similar mailing to the one in question in 2002 with no involvement from the company. The message of the original letter was still important and Procter & Gamble offered to support a repeat mailing. Neither Procter & Gamble nor the professor intended promoting any particular brand of oral mesalazine in this letter. Procter & Gamble did not consider that the letter promoted any brand of oral mesalazine and it was sorry if the letter had given some recipients that impression.

As the letter only referred to the class of medicine, mesalazine, and did not mention any particular brand, it could not be considered a promotional piece. AS7285 was a unique and internal reference number issued by Procter & Gamble which was assigned to an item when it was reviewed by its copy review team. As the mailing of this item was sponsored by Procter & Gamble it was reviewed to ensure it was factually correct and that the statement of sponsorship was legible. This was not a promotional piece for Asacol and therefore prescribing information was not necessary. Procter & Gamble denied a breach of Clause 4.1.

In Procter & Gamble's view, the letter maintained the high standard expected for communication within the medical community.

The branded prescribing of oral mesalazines was recommended by most prescribing guides. Despite this, in 2006 nearly 40% of oral mesalazine prescriptions nationally were still being written generically. Based on this Procter & Gamble considered that the message and the format of the letter were both relevant and tasteful and therefore not a breach of Clause 9.1.

The 'Dear Doctor' letter was a mailing from the professor and as such the views expressed therein belonged to him. The educational grant provided by Procter & Gamble was used to cover the postage costs and, as required by Clause 9.10, this sponsorship was declared on this letter. The letter did not refer to any particular brand of oral mesalazine.

Procter & Gamble considered that this letter could not be seen as disguised promotion and therefore there was no breach of Clause 10.1.

In response to a request for more information Procter & Gamble reiterated that the letter in question was initially written and mailed by the professor in 2002. The company enquired as to whether the professor would appreciate financial support in its re-printing and distribution by a third party. Procter & Gamble paid for these costs. The professor advocated re-sending the letter as he was committed to emphasising the importance of brand prescribing for continuity of care in inflammatory bowel disease. The importance of this message had already been highlighted in MIMS and the BNF and because of its relevance country wide, the letter was sent to health professionals throughout the UK. The list of recipients was decided by the professor. The letter was updated with information provided by Procter & Gamble to include the most recent statistics on branded prescribing. The professor was the author and final signatory of the letter. He had editorial control throughout.

The letter was not intended to promote a particular brand but to raise awareness of the importance of consistency of care in inflammatory bowel disease. Procter & Gamble therefore considered that the letter could not be seen as disguised promotion as the content was purely medical information.

In response to a further request for more information Procter & Gamble again stated that it did not consider that the letter at issue promoted Asacol. It did not mention any particular brand of oral mesalazine, therefore prescribing information was not necessary. Procter & Gamble regretted that the complainant was confused by the AS7285 reference, which was an internal certification reference number.

The letter had to be certified because Procter & Gamble had provided an educational grant to cover the mailing costs. As confirmed by the professor, acknowledgement of the source of funding for postage (not from the NHS) was simply to make this transparent rather than appear to be promotional. From discussions between the complainant and the professor it appeared that the nature and extent of the educational grant was initially not clear to the complainant, and had given him reason to complain. Clarification subsequently provided by the professor to the complainant had proven to be satisfactory to both parties.

Procter & Gamble had taken these insights very seriously and would be more specific on disclosing the extent of funding of an educational grant whenever future materials were developed.

In conclusion Procter & Gamble did not believe that the letter was in breach of Clause 4.1.

Procter & Gamble noted that it had previously argued

that the letter maintained the high standard expected for communication within the medical community:

- The issue regarding interchanging one oral mesalazine with another without proven equivalence in bioavailability was discussed widely by physicians caring for patients with inflammatory bowel disease. Both MIMS and the BNF noted that enteric coated mesalazine preparations should not be considered interchangeable.
- Often patients were inadvertently switched from a branded prescription to a generic one without their knowledge which could potentially increase the risk of relapse in stable patients. The letter therefore was intended to make physicians appreciate this risk.

Procter & Gamble thus considered that the content and format of the letter was both relevant and tasteful and therefore not in breach of Clause 9.1.

Procter & Gamble stated that the process by which the letter at issue was produced was:

- In August 2006, the professor initiated discussions with Procter & Gamble about the nature of prescribing mesalazine and the non-equivalence in bioavailability of available products.
- Procter & Gamble offered to fund the mailing of a letter on this topic to doctors.
- The educational grant was not directed to the professor himself.
- The professor had complete editorial control over the content of the letter and as such the views expressed in the letter were his.
- The professor's hospital had a very wide referral base given its responsibility as a tertiary referral centre which spread out across the UK. The professor acknowledged that the hospital did not have full details of the names and addresses of prescribing physicians across the country; therefore he relied upon the supplier assigned to carry out the mailing. Regrettably the communication on mailing coverage between the professor and the supplier (in which Procter & Gamble was not involved) was not ideal and did not allow each party to have a full appreciation of each other's interpretation of the reach of the hospital's wide referral base. This might have resulted in some 'overshoot of the mark'. As soon as this was realised, further mailing was stopped.

In conclusion, Procter & Gamble did not consider that the letter was disguised promotion and therefore there was no breach of Clause 10.1.

PANEL RULING

The Panel noted that the letter was about the general issue of prescribing oral mesalazine. Recipients were reminded that mesalazine preparations differed in their release characteristics and as such should not be considered interchangeable. Once a patient was maintained on one particular brand of mesalazine it was important that they remained on that brand and were not given generic prescriptions which would mean that they might receive a different brand. The Panel noted that the letter did not mention any particular brand of oral mesalazine either by name or by implication. In that regard, given the general nature of the letter, the Panel did not consider that it promoted Asacol. The letter thus did not require prescribing information for Asacol. No breach of Clause 4.1 was ruled (Case AUTH/1898/10/06 only). The letter also, therefore, did not constitute disguised promotion for Asacol. No breach of Clause 10.1 was ruled.

With regard to the distribution of the letter the Panel noted that the professor had relied upon the supplier assigned to carry out the mailing. The Panel considered that if this supplier had been appointed by Procter & Gamble the company should have briefed the supplier such that there was no misunderstanding as to whom the mailing was to be sent. It was not clear who generated the final mailing list and on what basis but it appeared that the mailing had gone to more people than the professor had originally envisaged. In that regard the Panel considered that Procter & Gamble might not have managed the project with enough care to ensure that high standards were maintained. In addition the Panel noted that Procter & Gamble had paid for the mailing costs. In that regard the statement that the letter had been sponsored by an educational grant was misleading. In the Panel's view it was beholden upon companies not only to declare their sponsorship of material but also to be very clear about the nature of the sponsorship. Overall high standards had not been maintained. A breach of Clause 9.1 was ruled.

Complaints received

Case AUTH/1898/10/06	**10 October 2006**
Case AUTH/1900/10/06	**12 October 2006**
Cases completed	**10 January 2007**

PRIMARY CARE TRUST CHIEF PHARMACIST/ ASSOCIATE DIRECTOR OF PUBLIC HEALTH v GLAXOSMITHKLINE

'Dear Practice Nurse' letter about Rotarix

The chief pharmacist and associate director of public health at a primary care trust complained that a 'Dear Practice Nurse' letter about Rotarix (rotavirus vaccine) was sent by GlaxoSmithKline to non-prescribers.

The Panel noted that the letter introduced Rotarix as the first gastroenteritis vaccine in Europe for infants from six weeks of age. Clinical data and details of the dose schedule within the context of UK routine childhood vaccinations were provided together with information about how to order the vaccine.

The Panel noted that the letter was one part of a co-ordinated mailing that targeted prescribers and administrators of paediatric vaccines. GlaxoSmithKline submitted that in all cases, as a minimum, the lead prescriber within each practice would have received information on Rotarix prior to the practice nurse letter in question being received.

The Panel noted GlaxoSmithKline's submission that within the UK approximately 800 nurse prescribers could prescribe from a full formulary. The majority of nurses could not prescribe particular medicines or vaccines unless a patient group direction had been authorized. The Panel considered that it was reasonable to provide the letter to practice nurses irrespective of whether they could prescribe the product given their role in the administration and ordering of vaccines. No breaches of the Code were ruled.

The chief pharmacist and associate director of Public Health at a primary care trust complained about a 'Dear Practice Nurse' letter (ref ROT/LTR/06/26848/1c) concerning Rotarix (rotavirus vaccine) sent by GlaxoSmithKline UK Ltd.

COMPLAINT

The complainant was extremely concerned that this letter was sent to non-prescribers; this issue had been raised by the practices the complainant worked with as none of the information seemed to have been sent to the prescribers themselves. The complainant asked if it was ABPI policy for companies to target non-prescibers without any information being provided to prescribers.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 9.1 and 12.1 of the Code.

RESPONSE

GlaxoSmithKline stated that the mailing was part of a co-ordinated communication that targeted both prescribers and administrators of paediatric vaccines. As such, GlaxoSmithKline denied breaches of Clauses 12.1 and 9.1.

GlaxoSmithKline explained that when Rotarix was launched at the end of May 2006 a letter, which included a parent's information leaflet, was sent to a wide range of interested and relevant health professionals including the lead paediatric vaccine GP in every practice, lead paediatric practice nurses, health visitors, paediatricians and consultants in communicable disease control. The same mailing was sent at the end of July to private GPs and in August to all UK paediatric nurses and paediatric gastroenterologists. A copy of the letter and the leaflet was provided.

A follow-up letter, the subject of this complaint, was sent on 27 September 2006 as a reminder that the vaccine was now available and could be ordered, if required, from the GlaxoSmithKline Customer Contact Centre. In order to audit follow-up responses, this mailing was targeted to UK primary care practices in three ways: in the first group of practices, all GPs and all practice nurses were sent the letter; in the second group the letter was sent to the lead paediatric GP and the lead paediatric vaccine nurse whilst in a third group of practices, no mailing was sent at all. There were approximately a third of UK primary care practices within each group. As such there would be variability in the extent of the mailing between practices, but GlaxoSmithKline stated that in all cases, at a minimum, the lead prescriber within each practice would have received information on Rotarix before the practice nurse received a letter.

Given the mailing strategy described above, there were 52 practices where the practice nurse mailing would have been sent to a branch surgery which fell into group two but where the main practice surgery would have fallen into group three. In that case a practice nurse might have received the follow-up mailing but not the lead paediatric vaccine prescriber. In all cases, however, the lead paediatric vaccine prescriber would have received the original launch mailing.

GlaxoSmithKline knew that practice nurses appreciated receiving information about new vaccines that they were likely to be involved with administering or discussing with parents. Given that Rotarix was the first rotavirus gastroenteritis vaccine in Europe for infants, and also given the potential public health benefits GlaxoSmithKline considered it important that prescribers and potential administrators of this vaccine should be made aware of it. There was no doubt that practice nurses were a relevant audience in both the letter and spirit of the Code.

With regard to prescribing there were currently about 800 accredited nurse prescribers in the UK who could

prescribe from a full formulary. In the majority of cases, however, practice nurses could not prescribe particular medicines or vaccines unless a patient group direction had been authorised within that practice or area population. A large majority of practice nurses were however involved with the administration and ordering of vaccines. As such, the purpose of the letter was to build on the initial launch mailing to lead paediatric vaccine prescribers in all practices to make nurses aware of the availability of Rotarix.

Given the complaint, GlaxoSmithKline assumed that the time lag between the launch mailings (which clearly covered the lead paediatric vaccine GP prescribers in all practices), and the practice nurse mailing in question, together with the strategy to variably target different practices meant that the complainant did not know about the launch mailings. This might have appeared to be the case to a greater extent if the practice fell within the 'second group' as described earlier.

Nevertheless, despite the extensive launch mailing it was clear that a practice nurse mailing was a legitimate exercise that complied with the Code. Nurses were professionals in their own right and promotion to them was a legitimate activity. GlaxoSmithKline had taken steps to ensure that a prescriber in every practice had received a mailing prior to the practice nurse mailing. Thus GlaxoSmithKline strongly refuted any breach of Clause 12.1 and thus Clause 9.1.

PANEL RULING

The Panel noted that the letter at issue introduced Rotarix as the first gastroenteritis vaccine in Europe for infants from six weeks of age. Clinical data was discussed and details of the dose schedule within the context of UK routine childhood vaccinations was provided. Information about how to order the vaccine was also provided.

The Panel noted that the letter was one part of a co-ordinated mailing that targeted prescribers and administrators of paediatric vaccines. GlaxoSmithKline had submitted that in all cases, as a minimum, the lead prescriber within each practice would have received information on Rotarix prior to the practice nurse letter in question being received.

The Panel noted GlaxoSmithKline's submission that within the UK approximately 800 nurse prescribers could prescribe from a full formulary. The majority of nurses could not prescribe particular medicines or vaccines unless a patient group direction had been authorized. The Panel considered that it was reasonable to provide the letter to practice nurses irrespective of whether they could prescribe the product given their role in the administration and ordering of vaccines. No breach of Clause 12.1 was ruled. High standards had been maintained; no breach of Clause 9.1 was ruled.

Complaint received **16 October 2006**

Case completed **15 December 2006**

CASE AUTH/1906/10/06

PARAGRAPH 17/DIRECTOR v SERVIER

Training material

During its consideration of Case AUTH/1889/8/06, some training material in the form of a slide set which instructed representatives on how to access hospital health professionals came to the Panel's attention. The Panel queried whether the material met the requirements of the Code which stated that briefing material must not advocate, either directly or indirectly, any course of action which would be likely to lead to a breach of the Code. The Panel was also concerned that the material did not maintain high standards and brought the industry into disrepute. The Panel decided to take the matter up as a fresh complaint in accordance with Paragraph 17 of the Authority's Constitution and Procedure.

The Panel was extremely concerned regarding the content of the training material, which did not refer at any point to the requirements of the Code. Whilst the Panel accepted that representatives needed to be told about hospital management structure and the status of those health professionals they were likely to encounter such discussions should be placed firmly within the context of the Code.

The Panel noted Servier's material advised representatives to 'Try to establish if there is a protocol for representatives to follow'. It was not made clear that the existence or otherwise of a protocol should be established at the outset, prior to or on entering a hospital. Nor was the importance of compliance with it stressed.

The Panel was very concerned that the material encouraged access to all levels of health professionals, appropriate administrative staff and others including secretaries, and all parts of the hospital without stating that such access must comply with the Code including the requirement that promotion be tailored to the audience. One slide stated 'Potentially access any grade of doctor!' and 'Access Ward Nurses themselves'. Another slide about bleeping referred to junior doctors without reminding the representatives that not all hospitals would allow them access to junior members of staff. A slide headed 'Other sources of information' listed, *inter alia*, security staff, cleaners and in conclusion 'ANYONE!' thus giving the impression that representatives could freely approach absolutely anybody in the hospital environment for information about health professionals. That was not so. No caveats appeared in the speaker notes. An additional slide, which appeared only in the speaker notes, was headed 'Alternative access places' and listed, *inter alia*, coffee shops, hospital restaurants, library and laboratories. The Panel queried whether it would ever be acceptable to access health professionals in, say, the hospital library in the absence of an express invitation to do so and bearing in mind any relevant hospital policy.

The Panel considered that the training material encouraged predatory behaviour in a hospital environment and advocated a course of action likely to lead to a breach of the Code. A breach of the Code was ruled. High standards had not been maintained and the material was likely to bring the industry into disrepute; breaches of the Code were ruled including Clause 2.

COMPLAINT

In Case AUTH/1889/8/06 the Panel was extremely concerned about whether some training material specifically for NHS project co-ordinators (NHSPCs) met the requirements of the Code. Clause 15.4 of the Code stated that representatives must ensure that the frequency, timing and duration of calls on health professionals, administrative staff in hospitals and health authorities and the like, together with the manner in which they were made did not cause inconvenience. The wishes of individuals on whom representatives wished to call and the arrangements in force at any particular establishment, must be observed. The training material described access to doctors, nurses and pharmacists in secondary care. Within a section headed 'Useful things to know…', 'Pharmacy', representatives were advised to 'Try to establish if there is a protocol for representatives to follow'. It was essential that representatives were aware of hospital policy regarding access. It was not made clear that this should be established at the outset. Reference was made to befriending secretaries as quickly as possible and building relationships with ward managers and sisters. No caution was expressed in relation to the relevant requirements of the Code in this regard.

In relation to ward nurses representatives were instructed to 'Spec on wards'. Representatives could 'access clinic nurses themselves' and 'access ward nurses themselves'. The presentation contained a slide listing all grades of nurses including student and auxiliary nurses. All grades of doctors had also been listed including medical students. Representatives were advised that the mess president might provide bleep numbers and although some advice was given regarding the use of bleeps, representatives were told that on wards they could 'Potentially access any grade of doctor!'. The presentation did not state that such access must comply with the Code in particular Clauses 15.2 and 15.4. Despite the wide range of health professionals referred to; consultants, pharmacists etc, there was no instruction to tailor promotion. In the Panel's view it was inappropriate for representatives to actively seek out medical students, student nurses or auxiliary nurses. Such staff were neither health professionals nor appropriate administrative staff. One slide stated that clinics/out patients and wards were to be treated like a GP practice. The Panel queried whether this was appropriate. A slide headed 'other sources of information' listed *inter alia*, switchboard, post room, posters, security staff, cleaners and in conclusion 'ANYONE!'. The Panel queried whether seeking information about health professionals and access to them from a cleaner, or the post room would ever be appropriate given the requirements of Clauses 15.2 and 15.4 of the Code.

Given its comments above the Panel queried whether the training material met the requirements of Clause 15.9 of the Code which stated that briefing material must not advocate, either directly, or indirectly any course of action which would be likely to lead to a breach of the Code. The Panel was also concerned that such material did not maintain high standards and brought the industry into disrepute contrary to Clauses 9.1 and 2. The Panel decided to take the matter up as a fresh complaint (case AUTH/1906/10/06) in accordance with Paragraph 17 of the Authority's Constitution and Procedure.

RESPONSE

Servier agreed that it was essential that representatives were aware that hospital protocols were to be followed at all times and took every opportunity to ensure that representatives were instructed to do so.

In the NHSPC training course, where the presentation that concerned the Panel was presented, another presentation on the Code was delivered, which clearly instructed and reminded representatives of their obligations.

Servier considered all training given to the representatives as instruction and not advice and the consequences for disobeying these instructions could be severe. The slide entitled 'Pharmacy' instructed representatives to make the pharmacy the 'First port of call' with further instruction to 'Try and establish if there is a protocol for representatives to follow'. This instruction was unambiguous. In addition, the Code training presentation required all representatives to have understood Clause 15 of the Code; the requirements of Clauses 15.2 and 15.4 were described verbatim. The instruction to try and establish if a protocol existed was therefore absolutely clear and reinforced on at least one other occasion in the training course. Representatives were therefore appropriately instructed in the requirements of Clause 15 on more than one occasion during this training and no breach had occurred.

Servier acknowledged that representatives were instructed to befriend secretaries and build relationships with ward managers as described by the Panel; it was not inappropriate for this to happen. Secretaries booked appointments for health professionals and it was therefore important for representatives to be on good professional terms with them in order to facilitate appropriate appointment making. Ward sisters increasingly influenced prescribing and were also often sources of key information such as how a representative might approach a health professional without causing offence or nuisance. Again these instructions to representatives must be taken in the context of the Code presentation which, *inter alia*, defined health professionals and described the requirements of Clause 18. The Panel would recall that, in addition, these requirements were reinforced by a bulletin from the chief executive. In light of all this instruction, given on numerous occasions to the representatives, a considerable amount of caution had indeed been expressed.

The slide that listed the grades of nurses and doctors was for the representatives' information only. It was inappropriate not to fully brief representatives on all potential professionals and training grades that they might encounter when performing their duties within the Code. However representatives were not asked or incentivised to call upon individuals who were not health professionals or appropriate administrative staff. In addition to this, the Code training presentation clearly stated who health professionals were as defined in the Code, thereby ensuring that inappropriate calling did not occur. Representatives were not encouraged to actively seek out medical students, student nurses and auxiliary nurses as alleged and thus no breach of Clause 15.9 had occurred.

Servier considered that a health professional's time was important and needed to be respected. Most hospital representatives came from primary care sales and would know the importance of this; as mentioned previously representatives were instructed to obey all local protocols. In terms of provision of care for patients, out-patient clinics were indeed similar to GP surgeries and thus similar instruction was appropriate. The suggestion that the care provided in a GP surgery was any less important than an out-patient clinic in a hospital was not a position that Servier endorsed.

The slide entitled 'Other sources of information' was designed to help the representatives understand where general information might be sourced. These 'other sources of information' would not have information about health professionals that might be of use to representatives, nor was this implied in Servier's training materials. Information that these professionals might provide could include the location of wards or offices and the like. The seeking of such information from these sources was not inappropriate.

The training presentation directly referred to by the Panel was had been certified as complying with the requirements of the Code. The certificate was provided. The training material was still in use. Another presentation giving instruction on access to health professionals was the Code presentation.

Servier believed that the presentation at issue complied with the Code and in particular did not breach or suggest actions that might result in a breach. Furthermore this presentation was given on the same course as a presentation reaffirming the representatives' responsibilities on the Code itself which was unequivocal on the requirements of the Code. In light of this Servier denied breaches of Clauses 15.9 and Clause 9.1.

Nothing within either briefing material would bring discredit upon or reduce confidence in the pharmaceutical industry and thus Servier did not believe that Clause 2 had been breached.

In response to a request for further information Servier provided the slides with speaker notes for the NHSPC presentation, advising that representatives at the course were given paper copies of the slides (not speaker notes) of both the 'Code training for ITP' and the NHSPC presentation. These were the only

presentations given to these representatives on this course with respect to accessing doctors.

The primary care representatives were also given the presentation 'Code Training for ITP' presentation both during the course and as a handout. In addition they were given a separate presentation on selling skills, copies of which were provided together with the speaker notes. They received no other training in respect to access to doctors.

All the representatives were given a copy of the latest Code and a copy of 'The Code in the Field' to ensure that they understood the Code and their responsibilities within it.

PANEL RULING

The Panel was extremely concerned regarding the content of the NHSPC training material. The slide set did not refer at any point to the requirements of the Code. Whilst the Panel accepted that representatives needed to be told about hospital management structure and the status of those health professionals they were likely to encounter such discussions should be placed firmly within the context of the Code. In particular the requirements of Clauses 15.2 and 15.4 should be made abundantly clear.

The Panel noted Servier's submission about the need to establish the existence of a hospital protocol. The Panel noted that the relevant reference appeared on a slide entitled 'Pharmacy', in the 'Hospitals, A Golden Opportunity' section of the NHSPC presentation, after the detailed lists of customers (doctors, pharmacists and nurses). It was not made clear that the existence or otherwise of a protocol should be established at the outset, prior to or on entering a hospital. Nor was the importance of compliance with it stressed. The speaker notes were silent on this point.

The Panel was concerned that when listing potential customers all grades of doctors, nurses and pharmacists were listed (including auxiliary nurses and medical students) without any reference to Clause 12 of the Code which required promotion to be tailored towards the audience.

The Panel was very concerned that the presentation encouraged access to all levels of health professionals, appropriate administrative staff and others including secretaries, and all parts of the hospital without stating that such access must comply with the Code. The Code was not referred to in the speaker notes. One slide stated 'Potentially access any grade of doctor!' and 'Access Ward Nurses themselves'. Another slide about bleeping referred to junior doctors without reminding the representatives that not all hospitals would allow them access to junior members of staff. A slide headed 'Other sources of information' listed, *inter alia*, security staff, cleaners and in conclusion 'ANYONE!' thus giving the impression that representatives could freely approach absolutely anybody in the hospital environment for information about health professionals. That was not so. No caveats appeared in the speaker notes. An additional slide, which appeared only in the speaker notes, was headed 'Alternative access places' and listed, *inter alia*, coffee shops, hospital restaurants, library and laboratories. The Panel queried whether it would ever be acceptable to access health professionals in, say, the hospital library in the absence of an express invitation from the doctor to do so and bearing in mind any relevant hospital policy.

The Panel considered that the training material encouraged predatory behaviour in a hospital environment and the slide set advocated a course of action likely to lead to a breach of the Code. A breach of Clause 15.9 was ruled. High standards had not been maintained and the material was likely to bring the industry into disrepute; breaches of Clauses 9.1 and 2 were ruled.

The Panel did not consider that the separate 'Code training for ITP' presentation was sufficient to negate the misleading impression given in the NHSPC slide set. Whilst the overall training provided to the representatives was relevant, each presentation had to stand alone with regard to compliance with the Code. Further, the 'Code training for ITP' presentation simply reproduced clauses of the Code and did not link the detailed examples given in the presentation at issue with the relevant clauses.

Proceedings commenced **25 October 2006**

Case completed **21 December 2006**

CASE AUTH/1907/10/06

GALEN v IVAX

Promotion of Mucodyne

Galen complained about the promotion of Mucodyne (carbocysteine) by Ivax alleging that it was inappropriate to cite Allegra *et al* (2006) in support of several claims for the product. Allegra *et al* studied Fluifort, a once daily oral dose of 2700mg of carbocysteine lysine salt monohydrate (equivalent to 1409mg of carbocysteine) for the prevention of acute exacerbations of chronic obstructive bronchitis. Mucodyne (carbocysteine), however, was licensed for oral administration in a dose of 2250mg, reducing to 1500mg, daily in divided doses. The dose of carbocysteine administered as Fluifort was thus not the same as that derived from the recommended doses of Mucodyne. Consequently, it was unacceptable to rely on clinical efficacy data generated on once daily doses of Fluifort to claim efficacy for multiple daily doses of Mucodyne.

In an advertisement headed 'Appearances can be deceiving' Allegra *et al* was cited as as evidence that 'Mucodyne reduces the hypersecretion and viscosity of mucus, thereby making it easier for the patient to clear mucus from the bronchial tree through expectoration', 'Use of Mucodyne results in: Carbocysteine vs placebo n=441, 43% reduction in days with acute illness p< 0.01, 40% reduction in antibiotic consumption p< 0.02, 51% (over two months) increase in delay to first exacerbation p=0.028 ' and Mucodyne 'Clears mucus to reduce COPD exacerbations'.

Galen alleged the absence of bridging pharmacokinetic, bioequivalence or clinical efficacy data rendered the claims misleading and in breach of the Code. Claiming an equivalent therapeutic response of Mucodyne to Fluifort in Allegra *et al*, exaggerated the risk/benefit ratio.

The Panel considered that Allegra *et al* studied a product which was in a different form, given in a different dose and with a different dosage schedule from Mucodyne. No data had been provided to show similarity between the product used in Allegra *et al* and Mucodyne. Thus in the Panel's view it was misleading to imply that Mucodyne would produce the results reported in Allegra *et al*.

The Panel considered it misleading to cite Allegra *et al* in support of the claim 'Mucodyne reduces the hypersecretion and viscosity of mucus thereby making it easier for the patient to clear mucus from the bronchial tree through expectoration'. Thus the Panel ruled a breach of the Code. The Panel did not consider that the reference to Allegra *et al* necessarily meant that the claim was not capable of substantiation or that the properties of Mucodyne had been exaggerated. No breaches of the Code were ruled.

The Panel noted the use of data from Allegra *et al* and considered that the advertisement implied that Allegra *et al* had shown that treatment with Mucodyne led to a 43% reduction in days with acute illness, a 40% decrease in antibiotic consumption and a 51% increase in delay to first exacerbation. This was not so. No data on Mucodyne had been provided. The Panel ruled breaches of the Code.

The Panel noted the claim that Mucodyne 'Clears mucus to reduce COPD exacerbations' and considered that it was misleading to cite Allegra *et al* in support of the claim which was specifically for Mucodyne. Thus the Panel ruled breaches of the Code. The Panel considered that its ruling also applied to two advertisements and the detail aid which also included the claim.

Galen Limited complained about the promotion of Mucodyne (carbocysteine) by Ivax Pharmaceuticals UK Limited. The items at issue were three journal advertisements (refs IV/MD/ADV1/01/06, IV/MD/ADV2/01/06 ad IV/MD/AD/11/05) and a leavepiece (ref IV/MD/DETAIL/LP/08/05).

COMPLAINT

Galen alleged that it was inappropriate to cite Allegra *et al* (2006) in support of several claims for Mucodyne because:

- Allegra *et al* studied the effectiveness of Fluifort (carbocysteine lysine salt monohydrate) (available in Italy) in the prevention of acute exacerbations of chronic obstructive bronchitis. Fluifort was given as a once daily oral dose of 2700mg. An English translation of the Fluifort summary of product characteristics (SPC) was provided.
- Mucodyne contained carbocysteine, not the lysine salt monohydrate, and was licensed for oral administration in a dose of 2250mg, reducing to 1500mg, daily in divided doses.
- The relative molecular weight of carbocysteine was 179.20, that of carbocysteine lysine was 343.39. Consequently, a dose of 2700mg of carbocysteine lysine monohydrate was equivalent to 1409mg of carbocysteine.
- It was evident that taking the equivalent of 1409mg of carbocysteine once a day was not identical to taking 2250mg daily in divided doses or 1500mg daily in divided doses. Consequently, it was unacceptable to rely on clinical efficacy data generated on once daily doses of 1409mg of carbocysteine in order to claim efficacy for multiple daily doses totalling 2250mg or 1500mg of carbocysteine.
- Despite repeated requests, Ivax had not provided bridging pharmacokinetic, bioequivalence or clinical efficacy data to demonstrate that once daily dosing of 1409mg carbocysteine was identical to multiple daily dosing totalling 2250mg/1500mg carbocysteine.

As the basis of its complaint, Galen noted that an advertisement headed 'Appearances can be deceiving' (ref IV/MD/ADV1/01/06) featured a number of claims referenced to Allegra *et al*:

(a) 'Mucodyne reduces the hypersecretion and viscosity of mucus, thereby making it easier for the patient to clear mucus from the bronchial tree through expectoration.'

(b) 'Use of Mucodyne results in: Carbocysteine vs placebo n=441, 43% reduction in days with acute illness p< 0.01, 40% reduction in antibiotic consumption p< 0.02, 51% (over two months) increase in delay to first exacerbation p=0.028.'

(c) Mucodyne 'Clears mucus to reduce COPD exacerbations'. (This claim was also featured in an advertisement headed 'Not everything needs to be this difficult' (ref IV/MD/ADV2/01/06), advertisement headed 'A clear way ahead in COPD' (ref IV/MD/AD/11/05), and detail aid (ref IV/MD/DETAIL/LP/03/06)

Galen alleged the claims breached Clause 7.2 of the Code. The absence of bridging pharmacokinetic, bioequivalence or clinical efficacy data to demonstrate once daily dosing of 1409mg carbocysteine was identical to multiple daily dosing totalling 2250mg/1500mg carbocysteine was viewed by Galen as sufficient grounds for this breach.

In addition, the claims did not comply with Clause 7.4. This would be rectified through provision of the relevant bridging data mentioned above.

By claiming an equivalent therapeutic response of Mucodyne to Fluifort in the Allegra *et al* paper, Clause 7.10 was contravened as the risk/benefit ratio had been exaggerated by adopting the claims of Fluifort.

In conclusion, Galen believed that the claims were inadequately supported by an unsuitable single source (Allegra *et al*) which formed the basis of several statements that were scientifically unjustifiable. Ivax had not provided bridging pharmacokinetic, bioequivalence or clinical efficacy data to demonstrate that once daily dosing of 1409mg carbocysteine was identical to multiple daily dosing totalling 2250mg/1500mg carbocysteine. Galen alleged that the material was inaccurate, unsubstantiated and misleading, in breach of Clauses 7.2, 7.4 and 7.10. Ivax had failed to substantiate its claims and had also refused to withdrawn these items.

RESPONSE

Ivax noted that Galen had stated that Allegra *et al* had used the Italian product, Fluifort, and that the SPC had been provided. This was incorrect as Allegra *et al* used a granulated product and not the commercialised syrup formulation from the SPC provided. The valid SPC had not been provided but Ivax noted that the SPC that it received stated that there was no difference between different dose forms.

Ivax noted that the statement from Galen that 'Mucodyne contains carbocysteine, not the lysine salt monohydrate and is licensed for oral administration in a dose of 2250mg, reducing to 1500mg, daily in divided doses', was correct as it related to Mucodyne but the SPC was incomplete as the sections relating to dosage were omitted. A complete Mucodyne SPC was provided.

Ivax noted that Galen had calculated the weight of carbocysteine in the carbocysteine lysine monohydrate Italian granulated product by simply using the molecular weight and the presumed weight of active in the sachet. Ivax believed that this was misleading as it ignored the excipient content; Allegra *et al* did not make it clear if the 2700mg referred to weight of the active or the overall weight of the sachet. In general, granular lysine salts had significant excipient content to make them stable. Ivax therefore could not confirm or refute this particular Galen statement but Ivax already presented this concern to Galen in writing.

Ivax noted Galen's statement that 'It is evident that taking the equivalent of 1409mg of carbocysteine lysine once a day was not identical to taking 2250mg daily in divided doses, or 1500mg daily in divided doses. Consequently, it was unacceptable to rely on clinical efficacy data generated on once daily doses of 1409mg of carbocysteine lysine in order to claim efficacy for multiple daily doses totalling 2250mg or 1500mg of Mucodyne (carbocysteine)'. This statement claimed that it was evident that the compounds were different. Ivax believed this to be misleading, because when medicines were compared, it was clear in the UK regulations that only relevant comparisons must be made and this had to take into account the absorption process and the active compound found in the plasma.

Lysine had been used for many years to increase the solubility and absorption of molecules and to reduce the gastrointestinal side effects for molecules such as aspirin. In the absorption process, the lysine was cleaved either at the site of absorption or in the plasma soon after absorption. In the case of lysine salts of carbocysteine, the molecule was well absorbed with or without lysine and as with other lysine derivatives, the lysine was inevitably cleaved leaving active carbocysteine in the plasma. This was clearly indicated on the Fluifort Syrup SPC supplied by Galen, which stated in section 5.2 that:

'*Carbocysteine lysine* is rapidly absorbed after the oral administration of a dose of 2.7g. The plasma peak is obtained after 1.5-2hrs, with a C_{max} of 11.2mcg/ml. The AUC is 43.3mcg/ml/hr. The pharmacokinetic curve of carbocysteine lysine is described by an open one compartment model. The volume of distribution is 60.4 litres.

The active substance has particular tropism for human pulmonary tissues, with a C_{max} and a $T_{1/2}$ in the mucus of 3.5mcg/ml and 1.8 hours respectively (dose at 2gm/day). A proportion of the active substance is also present in measurable concentrations in the mucus of the paranasal sinuses and ear for up to 8 hours after administration.

Carbocysteine lysine is eliminated with a plasma half life of about 1.5 hours.

The active substance and its metabolites are essentially eliminated via the kidneys. About 30-60% of the administered dose is excreted unchanged in the urine and the remainder is excreted in the form of various metabolites.

The bioavailability of carbocysteine lysine does not vary from one pharmaceutical form to another.'

The Fluifort SPC clearly stated that the lysine salt was absorbed, and that carbocysteine was the active form and that the bioavailability of carbocysteine was the same for different pharmaceutical forms.

Ivax submitted that Galen's statement that Ivax had not provided bridging pharmacokinetic, bioequivalence or clinical efficacy data to demonstrate that once daily dosing of 1409mg carbocysteine lysine was identical to multiple daily dosing totalling 2250mg/1500mg Mucodyne (carbocysteine)' was not true. Ivax had provided a detailed response to each of the Galen letters and in Ivax's letter of 4 August, a summary of the pharmacokinetic data was presented on the two SPC documents. Galen requested additional data, but this was included in the documents it had submitted in its complaint to the Authority.

As these data were the SPC and thus formed part of the licence documentation, Ivax was confident that the data were correct and in the absence of the SPC for the granulate product, Ivax assumed that the syrup had a similar pharmacokinetic profile as demonstrated in the Fluifort SPC.

When Ivax compared the pharmacokinetic profile of Mucodyne and carbocysteine lysine, it was seen that the profiles were virtually identical with a significant inter-individual variability. Ivax referred to a comparative table which provided evidence that 2.7g of carbocysteine lysine provided the same drug exposure as defined by area under the curve (AUC) as Mucodyne (carbocysteine). This was refuted in a letter from Galen on 21 September but in Ivax's response of 10 October, a full response was provided as the papers that were quoted were misrepresented.

When making a comparison, it was also important to compare the clinical efficacy in clinical studies. On 4 August, Ivax gave Galen details of a systematic meta-analysis review published in 2006 by the Cochrane collaboration that supported the conclusion of Poole and Black (1996). In this review, all clinical trials that met the selection criteria were discussed. In the results of this analysis, it was clearly demonstrated that whichever end point was reviewed, there was a consistent benefit from carbocysteine and that no additional efficacy was provided by any of the formulations of either N-acetylcysteine, carbocysteine lysine or Mucodyne carbocysteine.

Ivax submitted that the data included above clearly demonstrated that:

- Carbocysteine was the active compound in the plasma from both carbocysteine lysine and Mucodyne.
- Both products had similar drug exposure from doses of 750mg of Mucodyne (carbocysteine) and 2.7g of carbocysteine lysine.
- There were three formulations marketed of carbocysteine and they had been demonstrated to provide the same efficacy with no additional benefit conferred by any one formulation over the other by the Cochrane meta-analysis.
- The different carbocysteine formulations were regarded as synonyms as stated in the National Institute for Health and Clinical Excellence (NICE) handbook for general practitioners.
- The data required to support this position had already been provided to Galen.

Ivax therefore believed that its representation of the data in the material in question was appropriate and was supported by published data.

To provide a fair and accurate assessment, the exact wording of the Galen complaint and Ivax's detailed comments were listed, followed by a conclusion for each item.

1 Advertisement headed 'Appearances can be deceiving'

Galen alleged that Allegra *et al* was cited as proof that Mucodyne (carbocysteine) reduced the hypersecretion and viscosity of mucus from the bronchial tree through expectoration.

In this advertorial, the references for each paragraph were provided at the end, so as not to interrupt the text flow and to ensure the reference numbers were clearly visible. In its complaint, Galen omitted the complete text from this section of the advertisement, which was:

'Mucodyne is a class of treatment called mucolytics and is used for the treatment of respiratory tract disorders, which are characterised by excess mucus. Mucodyne reduces the hypersecretion and viscosity of mucus, thereby making it easier for patients to clear mucus from the bronchial tree through expectoration.'

This advertisement was written in the style where references were provided at the end of each paragraph so as not to interrupt the text. The paragraph in question was clearly supported by two references and not one as suggested by Galen.

The first reference was Allegra *et al* which was used to support the statement relating to mucolytics and their action. The specific comments relating to Mucodyne (carbocysteine) were supported by the Mucodyne SPC. Additionally, the prescribing information was also included.

Ivax therefore believed that this paragraph was appropriately referenced and was true and accurate. It did not believe it was in breach of the Code.

Galen stated that use of Mucodyne in accordance with the terms of the SPC and in particular the licensed posology would result in a 43% reduction in days with acute illness, a 40% reduction in antibiotic consumption and a 51% increase, over 2 months, in delay to first exacerbation.

Ivax believed that this statement was incorrect. The diagram described was clearly labelled Carbocysteine vs placebo with the Allegra *et al* reference. This statement was correct and true as carbocysteine was the active compound as stated on the Fluifort SPC.

The diagram was clearly labelled, as indicating that the study compared the effect of carbocysteine vs placebo. Ivax had already demonstrated that according to the SPC for carbocysteine lysine, the active ingredient in the plasma was carbocysteine and that the AUC for the dose used of 2.7g provided a similar AUC to carbocysteine derived from Mucodyne at a dose of 750mg.

As AUC was accepted as a measure of drug exposure, Ivax concluded that the two formulations would

provide a similar clinical effect. This was supported by the conclusions of the Cochrane Review that studied all forms of carbocysteine and no benefit in either efficacy response or dose response was seen for any of the formulations.

Ivax therefore concluded that this statement in the advertisement was written appropriately and was supported by references and it did not believe that it was in breach of the Code.

In relation to the claim that Mucodyne (carbocysteine) 'Clears mucus to reduce COPD exacerbations', Ivax stated that immediately above this statement was the Mucodyne logo and the indication that it contained carbocysteine which was clearly stated by Allegra *et al* paper to have these effects.

In view of the content of this advertisement and full data provided, Ivax believed that the data were provided in a balanced manner, were fully referenced and adequate data was provided for the health professional to be able to determine their own conclusion. In view of the comparative pharmacokinetics provided in the SPC, Ivax did not believe that this was a breach of the Code.

2 Advertisement headed 'Not everything needs to be this difficult'

The complaint failed to take into account the complete text from the advertisement and was taken out of context. It was also presented in a manner that failed to present the data in an accurate manner.

Allegra *et al* was used on three occasions in the advertorial.

The statement 'Mucodyne is a mucolytic agent and affects mucus-producing cells to reduce hypersecretion and viscosity of secretions, aiding elimination of mucus from the bronchial tree' was supported by two references. The Mucodyne SPC to support the Mucodyne element and Allegra *et al* to support the additional statements relating to mucolytics.

The statement 'Patients with excessive mucus production need to receive a higher starting dose of Mucodyne. The treatment is reviewed after a satisfactory response has been achieved (e.g. 4-6 weeks) after which a lower maintenance dose of Mucodyne can be taken for the duration of the troublesome symptoms' was clearly in agreement with the Mucodyne SPC and thus was consistent with the licence. As this advertorial contained prescribing information and was in compliance with the licence, Ivax did not add the SPC reference to all lines of text as this was unnecessary.

Allegra *et al* was used as it contained carbocysteine that produced a similar AUC to Mucodyne (carbocysteine) and the study demonstrated that treatment should be assessed after a 4-6 week period.

The statement Mucodyne (carbocysteine) 'Clears mucus to reduce COPD exacerbations' included the Mucodyne logo and was in accordance with the Mucodyne licence, therefore as above the SPC was not required to be referenced as API was included. The reference to Allegra *et al* was included to ensure consistency as it studied the effect of carbocysteine in patients with COPD.

When the text was reviewed in its entirety and the balance of the advertisement was taken into account, Ivax did not believe that the material breached the Code. All statements were consistent with both the Mucodyne SPC and Allegra *et al* and thus Ivax concluded it was appropriately discussed.

Ivax was also concerned that Galen continually referred to an assumed carbocysteine content even when no confirmatory data was available and when the documents it had provided clearly demonstrated that the dose used by Allegra *et al* provided the AUC and hence drug exposure equivalent to Mucodyne (carbocysteine).

3 Advertisement headed 'A clear way ahead in COPD'

This complaint was as the previous one as it contained prescribing information and statements made agreed with the Mucodyne SPC and Allegra *et al* and therefore would not be discussed separately.

4 Detail aid

The detail aid had never been amongst the list of items on which Galen based its complaint. This complaint was the first indication that Galen wished to make a complaint against this item, however, Ivax's response was the same as the 'Appearances can be deceiving' advertisement and the 'A clear way ahead in COPD' advertisement.

PANEL RULING

The Panel noted that Allegra *et al* reported the results of a placebo controlled trial designed to assess the prevention of acute exacerbations of COPD with carbocysteine lysine salt monohydrate. The active treatment consisted of a granular formulation of carbocysteine lysine salt monohydrate plus excipients, which was dissolved in about 50ml of water before intake once a day in the morning. Patients were not given the ready made syrup formulation described in the Fluifort SPC provided by Galen. This SPC stated that 'the bioavailability of carbocysteine does not vary from one pharmaceutical form to another'. The Panel considered that this statement might apply to carbocysteine lysine salt monohydrate. There was no similar statement in the Mucodyne SPC. The Panel considered that Allegra *et al* studied a product which was in a different form, given in a different dose and with a different dosage schedule from Mucodyne. No data had been provided to show similarity between the product used in Allegra *et al* and Mucodyne. Thus in the Panel's view it was misleading to imply that Mucodyne would produce the results reported in Allegra *et al*.

The Panel considered each of the items as follows.

1 Advertisement headed 'Appearances can be deceiving'

a) As noted above the Panel considered it misleading to cite Allegra *et al* in support of the claim 'Mucodyne reduces the hypersecretion and viscosity of mucus

thereby making it easier for the patient to clear mucus from the bronchial tree through expectoration'. Thus the Panel ruled a breach of Clause 7.2 of the Code. The Panel did not consider that the reference to Allegra *et al* necessarily meant that the claim was not capable of substantiation nor that the properties of Mucodyne had been exaggerated. No breach of Clauses 7.4 and 7.10 of the Code was ruled.

b) Use of data from Allegra *et al*

The Panel considered that the advertisement gave the impression that Allegra *et al* had shown that treatment with Mucodyne led to a 43% reduction in days with acute illness, a 40% decrease in antibiotic consumption and a 51% increase in delay to first exacerbation. This was not so. No data on Mucodyne had been provided. The Panel ruled breaches of Clauses 7.2, 7.4 and 7.10.

c) Claim that Mucodyne 'Clears mucus to reduce COPD exacerbations'

The Panel considered that it was misleading to cite Allegra *et al* in support of the claim which was specifically for Mucodyne. Thus the Panel ruled breaches of Clauses 7.2, 7.4 and 7.10.

2 Advertisements and detail aid including the claim 'Clears mucus to reduce COPD exacerbations'

The Panel considered that its ruling at 1(c) above applied to the two advertisements and the detail aid.

Complaint received **2 November 2006**

Case completed **10 January 2007**

CASE AUTH/1908/11/06

VOLUNTARY ADMISSION BY LILLY

Arrangements for a meeting

Lilly voluntarily advised the Authority that it had breached the Code in relation to a meeting for health professionals. The primary purpose was to meet with office holders of four organisations for overseas psychiatrists and in that regard facilitate a handover between the previous and newly appointed managers. The attendees discussed Lilly's potential partnership with the four groups, educational services that Lilly could provide and the further development of Lilly's current service offerings and support to these groups. There was no formal agenda.

The Panel noted that the meeting had been organised to introduce Lilly's new neuroscience manager to the four associations which made up 'A Great Partnership' ie the Sri Lankan Psychiatry Association, the British Indian Psychiatry Association, The British Pakistani Psychiatry Association and the British Arab Psychiatry Association. The meeting had been held at the request of the President of one of the associations who had verbally invited the other attendees at Lilly's request. It was unclear as to whether Lilly had specified who should be invited and it was not known whether the purpose of the meeting had been explained to potential attendees beforehand. Lilly provided details of the costs of the meeting. The Panel considered that the hospitality provided was on the limits of what the recipients would normally adopt if paying for themselves.

The Panel considered that it was not inappropriate for officers of the various overseas psychiatry associations to meet Lilly to discuss future partnership and support although the Panel questioned whether it was necessary for four officers of one association to attend. The Panel was further concerned that two of the ten attendees were not officers of any of the associations but were the spouses of others who were and who were at the meeting. The Panel considered that the two spouses, although both health professionals in psychiatry, did not qualify as delegates to the meeting in their own right and in that regard the meeting did not comply with the requirements of the Code. A breach of the Code was ruled. High standards had not been maintained and so the Panel ruled a breach of the Code.

Although noting its rulings above, the Panel considered that the meeting *per se* was not inappropriate; it had been held in a private room and had had a legitimate purpose. In that regard the Panel considered that it had not brought discredit upon the pharmaceutical industry.

Eli Lilly and Company Limited voluntarily advised the Authority that it had breached the Code in relation to a meeting.

As the admission involved potentially inappropriate hospitality, which was a serious matter, the Director decided that it had to be treated as a complaint (Paragraph 5.4 of the Constitution and Procedure referred).

COMPLAINT

Lilly stated that it in responding to a complaint about an independent medical meeting organised by 'A Great Partnership' (referred to in the complaint as the South Asian Forum) (Case AUTH/1896/10/06) it discovered that, connected with that meeting, one of its employees had organised another meeting for health professionals in a priate room. The meeting was attended by three Lilly employees, including the Lilly organiser, and took place on Friday, 8 September.

The primary purpose of the meeting was to facilitate a hand-over between the Lilly organiser and one of the other Lilly employees present, since the organiser was moving on to another role within Lilly.

The meeting was, in part, a promotional meeting for Zyprexa (olanzapine). Unfortunately, in contravention of both Clause 19.1 of the Code and Lilly's own standard operating procedures (SOPs), the dinner was not approved in the usual way. As a consequence, Lilly disciplined the organiser and investigations were continuing with respect to the other two employees present. Lilly regretted this very unfortunate incident and stated that it was committed to adhere to both the spirit and tenets of the Code.

When writing to Lilly, the Authority asked it to respond in relation to Clauses 2, 9.1 and 19.1 of the Code.

RESPONSE

Lilly stated that it had inadvertently made a mistake in its voluntary admission. During the course of the disciplinary investigations it discovered that none of Lilly's products were discussed at the meeting.

Lilly explained that pursuant to an announcement that its previous neuroscience manager would be moved to another role within the company and be replaced by another employee, the President of one of the associations asked to be introduced to the new neuroscience national sales manager. As Lilly had sponsored an independent meeting co-chaired between 'A Great Partnership' and the Royal College of Psychiatrists at the Marriott Hotel on Saturday, 9 September, it was considered appropriate to arrange the meeting to discuss the hand-over on the Friday night, as most of the attendees would have had to stay in the hotel for Saturday's meeting. Of the ten health professionals at the meeting on the Friday, nine were consultant psychiatrists and one was a ward sister at a psychiatric hospital. Four associations comprised 'A Great Partnership', ie the Sri Lankan Psychiatry Association (SLPA), the British Indian Psychiatry Association (BIPA), the British Pakistani Psychiatry Association (BPPA) and the British Arab Psychiatry Association (BAPA). The names, and where appropriate, the affiliations of each of the ten attendees were given.

The meeting costs were £947.95, broken down as follows: room hire, £250; dinner for 15 @ £28 per person, £420; drinks, £277.95.

The primary purpose of this meeting was to facilitate a hand-over between the previous and newly appointed neuroscience managers. It was arranged with key stakeholders of the four organisations forming 'A Great Partnership', to discuss Lilly's potential partnership with these four groups, educational services that Lilly could provide and the further development of Lilly's current service offerings and support to these groups. It was also intended to be a working dinner whereby changes in the pharmaceutical environment and the Code were discussed. There was no formal agenda for the meeting. The health professional who had requested the meeting verbally invited the others at Lilly's request. The attendees were selected by Lilly in consultation with the doctor who had requested the meeting and were primarily selected as office holders of the four associations. No materials were provided by Lilly to the attendees before or during the dinner.

In respect of Clause 19.1 of the Code, Lilly accepted that the hospitality provided might be considered to be disproportionate to the content of the meeting as the meeting was not promotional or scientific, but rather to introduce the four member groups of 'A Great Partnership' to Lilly's newly appointed neuroscience manager and to discuss Lilly's potential future partnership with these groups. In Lilly's view, however, the subsistence provided was appropriate and the costs involved did not exceed those which the recipients would normally adopt when paying for themselves. The venue was appropriate, ie a private room, and not lavish and, in accordance with the provisions of Clause 19.1, was attended only by health professionals. Lilly repeated that it arranged the meeting upon request from a health professional and decided on the format in light of the fact that the attendees would have had to be at the Marriott Hotel the following day for an educational meeting to start at 9am. It was therefore reasonable to expect that most of them would have had to stay overnight and would, in any event, have had to provide dinner for themselves on the night preceding the meeting, at the hotel. Lilly further repeated that this meeting was not approved in accordance with its own SOPs and that appropriate disciplinary action had been taken against the organiser to prevent a reoccurrence.

With regard to Clause 9.1, Lilly believed that it had maintained high standards at all times in respect of this meeting. As set out above, Lilly believed that it complied with the essence of Clause 19.1 (the venue was appropriate and private; the meeting was attended only by health professionals; the subsistence provided was not in excess of what the attendees would have paid for themselves). The meeting was, however, not approved in line with Lilly's SOP and the hospitality provided might be considered disproportionate to the content of the discussion, as a result of which Lilly had taken the appropriate disciplinary action. This did not amount to a failure to maintain high standards. The fact that the attendees would have had to be at the hotel for a scientific meeting the next day must be taken into account as well as the fact that Lilly discussed a future partnership with the four member groups of 'A Great Partnership'.

In respect of Clause 2, Lilly did not accept that any of its actions in respect of this meeting contravened this clause. A ruling of Clause 2 should be reserved for cases which required a sign of particular censure and Lilly believed that its actions in this case should not attract such censure. This meeting facilitated a genuine sharing of information between Lilly and the four member organisations in respect of Lilly's future partnership with these groups and changes in the current pharmaceutical environment and the Code were also discussed. Lilly repeated its arguments against a finding of Clause 9.1 and firmly believed that the meeting did not bring the industry into disrepute.

PANEL RULING

The Panel noted that the meeting had been organised to introduce Lilly's new neuroscience manager to the four associations which made up 'A Great Partnership' ie the Sri Lankan Psychiatry Association, the British Indian Psychiatry Association, The British Pakistani Psychiatry Association and the British Arab Psychiatry Association. The meeting had been held at the request of the President of one of the associations who had verbally invited the other attendees at Lilly's request. It was unclear as to whether Lilly had specified who should be invited and it was not known whether the purpose of the meeting had been explained to potential attendees beforehand.

The Panel noted that the total cost of the meeting for the thirteen attendees was £947.50 although this included a charge of £56 for two meals which were not taken. Thus, taking the cost of these two meals into account the cost per head for those who attended was £68.61 including the room hire charge of £250. The Panel considered that this was on the limits of what the recipients would normally adopt if paying for themselves.

The Panel considered that it was not inappropriate for officers of the various overseas psychiatry associations to meet with Lilly to discuss future partnership and support, although the Panel questioned whether it was necessary for four officers of one of the associations to attend. The Panel was further concerned that two of the ten attendees were not officers of any of the associations but were the wives of others who were and who were at the meeting. The Panel considered that the two spouses, although both health professionals in psychiatry, did not qualify as delegates to the meeting in their own right and in that regard the meeting did not comply with the requirements of Clause 19.1. A breach of that Clause was ruled. High standards had not been maintained and so the Panel ruled a breach of Clause 9.1 of the Code.

Although noting its rulings above, the Panel considered that the meeting *per se* was not inappropriate; it had been held in a private room and had had a legitimate purpose. In that regard the Panel considered that it had not brought discredit upon the pharmaceutical industry. No breach of Clause 2 was ruled.

Proceedings commenced 3 November 2006

Case completed 20 December 2006

CASE AUTH/1909/11/06 *NO BREACH OF THE CODE*

MEDICAL REPRESENTATIVE v ASTRAZENECA

Arrangements for meetings

A medical representative from an unnamed company alleged that certain meetings held by AstraZeneca were in breach of the Code.

The complainant referred to a dermatology meeting held at a sports club in October. Although the meeting was held in a private room, the wall that separated the room from the bar area was made of glass panels thus allowing members of the public to see the exhibition stands. Part of the slide presentation was also visible from the bar area.

The complainant also alleged that at least eight other meetings at various surgeries in the same area, that were credited as educational events, were just a means of raising funds.

With regard to the dermatology meeting, the Panel noted AstraZeneca's submission that it had not taken place on the date alleged; the meeting had been postponed and held instead in November, after the complaint was received. The Panel noted the inconsistencies between the complainant's description of the venue and AstraZeneca's. On the information before it the Panel considered that there was no evidence to show that when the meeting was held, members of the public could see exhibition stands or the slide presentation as alleged. No breach of the Code was ruled.

With regard to the meetings held at various surgeries, the Panel noted that AstraZeneca had submitted data to show that each of ten meetings held over a 3 month period (July-September 2006) was a promotional meeting. The subsistence provided appeared not to be unacceptable and no room hire had been paid. There was no evidence to show that the meetings were a means of raising funds with no educational content as alleged. No breach of the Code was ruled.

A medical representative from an unnamed company alleged that certain meetings held by AstraZeneca UK Limited were in breach of the Code.

COMPLAINT

The complainant stated that a dermatology meeting was held at a named sports club on a given date in October. The meeting was in a private room but the room contents and exhibition stands of a number of representatives could clearly be seen from the large bar area because the dividing room wall was made of large glass panels. It was also adjacent to a large restaurant. The meeting attracted a great deal of interest from the general public due to the subject and the high degree of visibility. Parts of the slide presentation were also visible from the bar area.

The complainant further stated that there had been at least eight meetings at various surgeries in the same area that were credited as educational events for

doctors, but in reality were just a means of raising funds with no educational content.

When writing to AstraZeneca, the Authority asked it to respond in relation to Clauses 2, 9.1, 19.1 and 20.1 of the Code.

RESPONSE

AstraZeneca did not consider that there had been any breach of the Code. The company was concerned, however, regarding the nature of the complaint as it was aware of some inter-company issues at a local level.

Meeting at a sports club

AstraZeneca stated that although it had planned to sponsor a lecture by a local consultant dermatologist in October the event was postponed some time ago and actually took place in November, after the complaint was raised. No event took place at the sports club on the date in question, either sponsored by AstraZeneca or by any other pharmaceutical company.

Following receipt of the complaint and subsequent discussions with the local representative, their line manager and the manager of the venue, a site visit was conducted in November by the representative and the consultant dermatologist. From this visit, the following details emerged:

- The sports club was a private tennis club, which provided a private room with conference facilities for use by the local community. It could not be described as a 'professional sporting venue' and so was considered an acceptable venue within AstraZeneca's External Meetings Policy.
- The private room was completely enclosed and separated from the small bar area and restaurant by a single dividing wall, which comprised half-height plasterboard and half-height smoked glass. It was therefore not possible to see clearly into the meeting room from the public area. The entrance doors contained full-height smoked glass-panelling.
- The other three walls were of solid brick.
- The back of the projection screen faced the public areas; the exhibition area was at the far end of the room away from the door.
- For future meetings additional screens would be placed in front of the glass doors to avoid any inadvertent sight of the slides by the public when the doors were opened. These screens were in place for the meeting in November.

AstraZeneca therefore considered that no *prima facie* case had been established. The complaint was misleading as it referred to a meeting in the past tense, which was alleged to have taken place in October when no such meeting had occurred.

Other meetings in the local area

The complainant had not provided specific details or dates for the meetings and so it had not been possible to make specific enquiries, however the company database showed that there were 10 meetings held inside GP surgeries in the three main postal bricks during the period July, August and September 2006. Summary details were provided. All the meetings were promotional run by AstraZeneca representatives within the relevant product licence. Appropriate subsistence, within AstraZeneca's Corporate Governance Policy limits was provided; no payments were made to speakers or for the room hire, therefore the company refuted the allegation that these meetings were a means of raising funds. AstraZeneca therefore denied any breach of Clauses 2, 9.1 and 19.2 of the Code.

PANEL RULING

The Panel noted that the complaint involved, *inter alia*, a dermatology meeting at the sports club in October. AstraZeneca submitted that the meeting had not taken place that month; it had been postponed and held instead in November after the complaint was received. The Panel was concerned that the representative holding the meeting appeared not to have visited the venue to assess its suitability until after receipt of the complaint. Nonetheless that visit had shown the need for screens to be placed by the glass doors into the exhibition room and, according to AstraZeneca, this had been done when the meeting was held. The Panel noted the inconsistencies between the complainant's description of the venue and Astra Zeneca's. On the information before it the Panel considered that there was no evidence to show that when the meeting was held, members of the public could see exhibition stands or the slide presentation as alleged. No breach of Clauses 2, 9.1 and 20.1 was ruled.

With regard to the meetings held at various surgeries, the Panel noted that AstraZeneca had submitted data to show that each of ten meetings held over a 3 month period (July-September 2006) was a promotional meeting. The subsistence provided appeared not to be unacceptable and no room hire had been paid. The Panel thus considered that there was no evidence to show that the meetings were a means of raising funds with no educational content as alleged. No breach of Clauses 2, 9.1 and 19.1 was ruled.

Complaint received	**3 November 2006**
Case completed	**30 November 2006**

PRIMARY CARE TRUST HEAD OF MEDICINES MANAGEMENT v JANSSEN-CILAG

Memory stick as promotional aid

The head of medicines management at a primary care trust complained about a card he had received from Janssen-Cilag offering him a computer memory stick simply for seeing one of the company's representatives. All he needed to do was send the card back and the representative would bring the memory stick with them at the time of the appointment.

The picture of the memory stick on the reply card showed that it featured the name of Risperdal Consta. The complainant alleged that this was in breach of Clause 18 of the Code which stated: 'They (ie gifts) must not bear a product name, but may bear a corporate name'.

The Panel noted that the reply paid card offering the memory stick gave the recipient a boxed space in which to write the best time for a representative to call. Next to the box was the statement 'A representative will deliver this item, but you are under no obligation to grant an interview'. In this regard the text on the reply paid card had followed the advice given in the Code's supplementary information. No breach of the Code was ruled.

The memory stick bore the product name Risperdal Consta. This was not unacceptable; promotional aids could bear the brand name or the non-proprietary name of a medicine. (The Panel noted that the complainant had, in error, referred to the requirements for medical and educational goods and services which could not bear a product name.) No breach of the Code was ruled.

The head of medicines management at a primary care trust complained about the offer of a memory stick by Janssen-Cilag Ltd in connection with the promotion of Risperdal Consta (risperidone, long-acting injection).

COMPLAINT

The complainant stated that he had received a card from Janssen-Cilag offering him a computer memory stick simply for seeing one of the company's representatives. All he needed to do was send the card back and the representative would bring the memory stick with them at the time of the appointment.

The picture of the memory stick on the reply card showed that it featured the name of Risperdal Consta. The complainant considered that this was in breach of Clause 18 of the Code which stated: 'They (ie gifts) must not bear a product name, but may bear a corporate name'. The complainant would therefore expect the company's name to appear on the memory stick but not a product name.

When writing to Janssen-Cilag, the Authority asked it to respond in relation to Clauses 15.3 and 18.1, paying particular attention to the supplementary information to Clause 15.3 on items delivered by representatives.

RESPONSE

Janssen-Cilag stated that the complaint related to a mailing sent on 2 and 3 November to a target audience of psychiatrists at specialist registrar level and above, and also to medical and pharmaceutical advisors.

The mailing offered a memory stick which cost £5.60 (excluding VAT), with a similar perceived value to the recipient. The memory stick to be provided was blank.

The memory stick was a promotional aid and conformed with all the requirements of Clauses 18.1, 18.2 and 18.3 of the Code in that it was inexpensive, relevant to the recipient's work and within the required price range. Further Clause 18.3 allowed for a brand name to be included on the promotional aid.

Although the reply paid card specified that a representative would deliver the memory stick, it also stated that there was no obligation to grant an interview. The offer therefore complied with the requirements of Clause 15.3.

PANEL RULING

The Panel noted that the complainant had implied that representatives were using the memory sticks as inducements to gain an interview. The complainant was also concerned that the memory stick bore the name of a medicine.

The reply paid card offering the memory stick gave the recipient a boxed space in which to write the best time for a representative to call. Next to the box was the statement 'A representative will deliver this item, but you are under no obligation to grant an interview'. In this regard the text on the reply paid card had followed the advice given in the supplementary information to Clause 15.3, Items delivered by Representatives. No breach of Clause 15.3 was ruled.

The memory stick bore the product name Risperdal Consta. This was not unacceptable; Clause 18.3 referred to promotional aids bearing the brand name or the non-proprietary name of a medicine. (The Panel noted that the complainant had, in error, referred to the requirements for medical and educational goods and services when he had stated that they could not bear a product name.) No breach of Clause 18.3 was ruled.

Complaint received	**9 November 2006**
Case completed	**11 December 2006**

CASE AUTH/1918/11/06

VOLUNTARY ADMISSION BY AMGEN

Promotion of prescription only medicine to the public

Amgen voluntarily admitted promoting Aranesp (darbepoetin alfa), a prescription only medicine, to the public.

As the matter related to a potentially serious matter, promotion of a prescription only medicine to the public, it was taken up and dealt with as a formal complaint under the Code in accordance with the Constitution and Procedure.

Amgen described events that took place at The National Kidney Foundation's (NKF's) annual conference October 2006. The NKF was a patient organisation and its conference was usually attended by patients and health professionals. Amgen had exhibited at the conference; its representative had set up the stand the night before the meeting in a room which he thought was away from the public. The representative therefore used branded material mistakenly thinking that the public would not see it. The exhibition started the next day at 9am. By 9.30am the representative realised that the area in which his stand was displayed was accessible to the public. He removed the branded material and telephoned head office to explain his mistake.

The Panel noted that Aranesp branded material had been displayed for a short time at a meeting of the NKF. The NKF was a UK charity run by kidney patients for kidney patients although its annual conference was usually also attended by health professionals. In the Panel's view the representative should have known that the conference audience in the area where he had his stand would have included patients/public and so he should have taken extra precautions to ensure that they did not see any branded material. It was not acceptable to assume when a mixed audience was present that a particular exhibition space would only be accessible to health professionals. As acknowledged by Amgen, a prescription only medicine, Aranesp, had been promoted to the public. The representative had thus not maintained a high standard of ethical conduct. Breaches of the Code were ruled. The Panel noted the representative's prompt action in removing branded items from his stand once he realised his mistake. The Panel considered that the circumstances thus did not warrant a ruling of a breach of Clause 2 of the Code.

Amgen Limited made a voluntary admission concerning the promotion to the public of Aranesp (darbepoetin alfa), a prescription only medicine.

Paragraph 5.4 of the Authority's Constitution and Procedure stated that the Director should treat such an admission as a complaint if it related to a serious breach of the Code. Promotion of a prescription only medicine to the public was regarded as a serious matter and the Director accordingly decided that the admission must be treated as a complaint.

COMPLAINT

Amgen described events that took place at the National Kidney Foundation (NKF) national conference on 14 October 2006, involving one of its representatives.

The NKF was a patient organisation that held an annual conference supported by the pharmaceutical industry. The conference was usually attended by patients and health professionals. It was common practice for this event to be attended by representatives as long as there was no marketing, in any form, of medicines to the public. However, Amgen's representative had inadvertently used branded materials and a branded exhibition banner in an area open to the general public. This was corrected immediately upon learning that the area was not restricted to health professionals.

The representative had set up his stand the night before the meeting, under the impression that company exhibition stands were in a separate room away from the public, whilst the patient advocacy group stands were set up in the main foyer. The representative therefore used a branded exhibition banner mistakenly thinking that the public would not see it. The exhibition started the next day at 9am. By 9.30am the representative realised that the area in which his stand was displayed was accessible to the public. He removed the branded material and branded banner and telephoned Amgen head office to explain his mistake.

Amgen apologised for potentially exposing members of the public attending the conference to branded materials and noted that it strove to abide by the Code in all matters. Amgen would make every effort to ensure that such a mistake did not happen again.

When writing to Amgen, the Authority asked it to respond in relation to Clauses 2, 15.2 and 20.1 of the Code.

RESPONSE

Amgen explained that the conference facilities were arranged in such a way that the industry stands were in a room that appeared to be completely separate from the rest of the meeting. Therefore, the representative was under the erroneous impression that the room with the stands in was for health professionals only, and would not be accessed by the general public. Given that the NKF meeting focussed not only on patients but also on health professionals this was not an unreasonable assumption.

The representative arrived at 9am to a stand that had been erected the night before. Shortly before 9.30am, the representative was asked to pose in front of his stand for some NKF publicity photographs. This made him carefully reassess the contents of the stand and also made him look, for the first time, at the contents of other stands in the room. He immediately realised that branding had been excluded from other stands because the room was, indeed, accessible to all conference delegates, including members of the general public. The banner and promotional materials were removed immediately; this was

approximately half an hour after the start of the meeting, and only a few minutes after the main conference start time of 9.30am.

In the short period of time that the banner had been in place, the representative was confident that only a handful of delegates had passed by the stand. Although it was not possible to state how many of these delegates were health professionals or patients, Amgen could verify that exposure of branded material to the public was very limited.

With regard to Clause 20.1, Amgen fully understood that prescription only medicines must not be promoted to the public. It noted that there was no malice aforethought on its part and the philosophy behind Clause 2 was reinforced during its sales training.

Amgen was aware that, under Clause 2, promotional activities must not be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry.

Whilst Amgen recognised that promotion to the public was a serious matter, it was confident that, in this case, only a limited number of people passed through the room during this period (single figures). The branded materials in question were displayed inadvertently and the error was corrected as soon as it was recognised. Therefore Amgen did not believe the inadvertent display of branded materials, an error that was corrected as soon as it was recognised, had, in this case, brought the industry into disrepute.

All Amgen representatives were fully conversant with the Code and aware of the need to maintain high ethical standards as outlined in Clause 15.2; indeed, the representative's remedial/corrective action to remove the offending materials was entirely consistent with someone upholding Amgen's high ethical standards.

The items on display at the Amgen stand included materials for both patients and health professionals. Patient materials were displayed so that health professionals could see what materials Amgen provided patients with kidney disease.

PANEL RULING

The Panel noted that Aranesp branded material had been displayed for a short time at a meeting of the National Kidney Foundation. The NKF was a UK charity run by kidney patients for kidney patients although its annual conference was usually also attended by health professionals. In the Panel's view the representative should have known that the conference audience in the area where he had his stand would have included patients/public and so he should have taken extra precautions to ensure that they did not see any branded material. It was not acceptable to assume when a mixed audience was present that a particular exhibition space would only be accessible to health professionals. As acknowledged by Amgen, Aranesp branded material had been on open view in an exhibition area accessible to the public; a prescription only medicine had thus been promoted to the public. A breach of Clause 20.1 was ruled. The representative had thus not maintained a high standard of ethical conduct, a breach of Clause 15.2 was ruled. The Panel noted the representative's prompt action in removing branded items from his stand once he realised his mistake. The Panel considered that the circumstances thus did not warrant a ruling of a breach of Clause 2 of the Code which was reserved to indicate particular censure.

Proceedings commenced **15 November 2006**

Case completed **10 January 2007**

INSULIN DEPENDENT DIABETES TRUST v NOVO NORDISK

Advertisement in Diabetes Breakthrough

The Insulin Dependent Diabetes Trust complained about an advertisement placed by Novo Nordisk in Diabetes Breakthrough, the magazine of the Juvenile Diabetes Research Foundation. Novo Nordisk explained that most copies of the magazine were sent to health professionals but some did go to the public.

The complainant stated that although Novo Nordisk was not directly advertising a product in particular, and most of the advertisement was about the company, the statement '… you need to be able to count on the company that supplies your medicine' advertised its products in general. It was a form of direct to consumer advertising of diabetes products made by Novo Nordisk which was sufficient to cause people to request a specific brand of insulin from their clinician.

The Panel noted that the advertisement featured a photograph of a young woman and the headline 'changing how we see your diabetes'. The Novo Nordisk company logo was in the bottom right hand corner. The text of the advertisement acknowledged the difficulties of living with diabetes and stated that Novo Nordisk wanted to help. The reader was told, *inter alia*, that the company would supply the necessary medicine and lead in the search for a cure; it would ensure diabetics had access to the care they needed and be ethical and responsible in its business.

The Panel accepted that the advertisement might encourage patients to discuss Novo Nordisk's products with their doctor but it did not encourage patients to ask their doctor to prescribe a specific medicine. The Panel ruled no breach of the Code.

The Insulin Dependent Diabetes Trust complained about an advertisement (ref INS/625/0806) placed by Novo Nordisk Limited in Diabetes Breakthrough, issue 37, the magazine of the Juvenile Diabetes Research Foundation. Novo Nordisk stated that Diabetes Breakthrough had a print run and circulation of about 10,000. 8,000 copies were sent to 1,600 health professionals (5 copies to each for distribution to colleagues). Over 700 were mailed directly to a database and the remaining copies were distributed through Novo Nordisk's head office and regional offices in response to enquiries and passed out to the general public and targeted audiences at various events.

COMPLAINT

The complainant stated that whilst Novo Nordisk was not directly advertising a particular product, it was advertising its medicines to people with diabetes. Although most of the advertisement was advertising the company, the statement '… you need to be able to count on the company that supplies your medicine' was actually advertising its products. It was a form of direct to consumer advertising of diabetes products made by Novo Nordisk which was sufficient to cause people to request a specific brand of insulin from their clinician.

When writing to Novo Nordisk, the Authority asked it to respond in relation to Clause 20.2 of the Code.

RESPONSE

Novo Nordisk stated that it tried to have a good relationship with all patient groups relevant to the therapy areas it was involved in. Novo Nordisk did not receive any complaints regarding this advertisement directly from any patient groups.

This corporate advertisement was designed to promote Novo Nordisk as a responsible pharmaceutical company that did more than just manufacture and supply medicines. The advertisement was intended to raise the awareness of Novo Nordisk's commitment to diabetes and its commitment to searching for a cure. Until a cure was found, Novo Nordisk would like to offer patients and health professionals the medicine they needed, support the care that patients needed and improve the view people had of the disease and of diabetics. The advertisement was not intended to increase the sale of any of Novo Nordisk's products but to increase the goodwill towards the company.

Novo Nordisk believed stating '… you need to be able to count on the company that supplies your medicine' should be read as saying there was more to a pharmaceutical company such as Novo Nordisk than manufacturing the medicines people were using. The emphasis of that sentence was on 'company' and not 'medicine'. And this was a general reference to all responsible pharmaceutical companies.

As no promotional claims were made about any of Novo Nordisk's products and no products were mentioned by name, it did not believe this corporate advertisement would cause people to request a specific brand of insulin from their clinician.

Novo Nordisk did not consider that the advertisement was in breach of Clause 20.2 of the Code.

PANEL RULING

The Panel noted that the advertisement featured a photograph of a young woman and the headline 'changing how we see your diabetes'. The Novo Nordisk company logo was in the bottom right hand corner. The text of the advertisement acknowledged the difficulties of living with diabetes and stated that Novo Nordisk wanted to help. The reader was told, *inter alia*, that the company would supply the necessary medicine and lead in the search for a cure; it would ensure diabetics had access to the care they needed and be ethical and responsible in its business.

Novo Nordisk had placed the advertisement and marketed medicines for diabetes. The Panel

considered that the advertisement raised the awareness of Novo Nordisk's corporate interest in the therapy area. The advertisement might facilitate the market development of Novo Nordisk's products.

The Panel noted the requirements of Clause 20.2 of the Code that information about medicines which was made available to the general public must be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. The Panel accepted that the advertisement might encourage patients to discuss Novo Nordisk's products with their doctor but it did not encourage patients to ask their doctor to prescribe a specific medicine. The Panel ruled no breach of Clause 20.2 of the Code.

Complaint received **20 November 2006**

Case completed **3 December 2006**

CASE AUTH/1922/11/06

VOLUNTARY ADMISSION BY GLAXOSMITHKLINE

Use of out of date prescribing information

GlaxoSmithKline voluntarily informed the Authority that out of date prescribing information had been used in Avandamet (rosiglitazone/metformin) advertisements from August 2006 until November 2006. As the Director considered that this was a potentially serious matter it was taken up and dealt with as a complaint under the Code in accordance with the Constitution and Procedure.

The Panel noted that for approximately three months Avandamet prescribing information had not referred to macular oedema as a serious but rare side effect. Given the theoretical implications for patient safety the Panel ruled breaches of the Code. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

GlaxoSmithKline UK Ltd voluntarily informed the Authority that out of date prescribing information had been used in Avandamet (rosiglitazone/metformin) advertisements from August 2006 until November 2006.

The action to be taken by the Authority in relation to a voluntary admission was set out in Paragraph 5.4 of its Constitution and Procedure which stated that the Director should treat the matter as a complaint if it related to a potentially serious breach of the Code or if the company failed to take action to address the matter. The Director considered that using incorrect prescribing information for a long period was a potentially serious matter and that the admission must accordingly be treated as a complaint.

COMPLAINT

GlaxoSmithKline stated that it considered itself to have been in breach of Clause 4 of the Code with respect to providing the most up-to-date prescribing information for advertisements for Avandamet.

The prescribing information was updated in August 2006, but the prescribing information dated April 2006 was used. This error was brought to GlaxoSmithKline's attention by Takeda in November. GlaxoSmithKline's normal procedure would be for the new prescribing information to be sent to the advertising agency and for the advertisement to be certified with a new code. GlaxoSmithKline stated that this was a one-off error, which occurred around a time of high staff turnover. GlaxoSmithKline immediately updated its procedures, to ensure that a change in staff would not cause the same error to recur. It had liaised with its advertising agency to ensure immediate insertion of the current prescribing information into all future advertisements.

Given the nature of the change to the prescribing information, GlaxoSmithKline did not consider that patients would have been put at serious risk.

GlaxoSmithKline invited the Authority to review the prescribing information for Avandia and Avandamet against the respective summaries of product characteristics (SPCs).

GlaxoSmithKline very much regretted the breach and reassured the Authority that it had taken appropriate steps to avoid any repeat of this error.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 2, 4.1 and 9.1 of the Code.

RESPONSE

GlaxoSmithKline acknowledged that the out of date prescribing information had been used in 84 advertisements from 30 August 2006 until the end of November 2006; a list of the relevant publications was provided. GlaxoSmithKline therefore conceded a breach of Clause 4.1 as per its voluntary admission.

GlaxoSmithKline's standard procedure was that if there was a change to the SPC, the prescribing information was updated and certified, and a unique identifying number was raised for each size of advertisement requiring the updated prescribing information. A job bag was created, containing the new advertisement with the updated prescribing information, which was then reviewed by the medical

adviser, scientific adviser and marketing manager. The item was then certified by the medical adviser and the marketing manager and archived. GlaxoSmithKline provided the standard operating procedure 'Approval process for promotional items'. The updated advertisements were then sent to the advertising agency for placement.

In this instance, updated prescribing information was certified on 31 August 2006 following an update to the SPC in August. The main change to the prescribing information was the inclusion of macular oedema as a rare side effect. GlaxoSmithKline had already sent a 'Dear Doctor' letter (dated 20 December 2005) to alert prescribers to the case reports of macular oedema and inform them that the regulatory authorities were reviewing this new safety concern. Given that GlaxoSmithKline had proactively communicated the safety concern to all prescribers prior to changes to the SPC and that the main change to the prescribing information was the inclusion of a rare, albeit serious, adverse event with an incidence of greater than or equal to 1/10,000 and less than 1/1000, GlaxoSmithKline did not believe that either patient safety or confidence in the pharmaceutical industry had been compromised.

However, there was an oversight by an individual within GlaxoSmithKline, who did not create job bags for new advertisements with the updated prescribing information. This person had now been retrained and all others with this responsibility had been reminded of the importance of following the established process. This was an isolated incident; the prescribing information on all other promotional material created since August 2006 was current.

GlaxoSmithKline sincerely regretted this incident and submitted that when it had been brought to its attention by a competitor, it rapidly ascertained the scope of the problem and took immediate action to remedy it. GlaxoSmithKline was confident that it had a robust system in place and had demonstrated this in the course of this response. As such GlaxoSmithKline denied a breach of either Clause 9.1 or Clause 2. GlaxoSmithKline detailed the differences between the April and August prescribing information.

PANEL RULING

The Panel noted that out of date prescribing information had been used for approximately three months; the information given had not referred to macular oedema as a serious but rare side effect. Given the theoretical implications for patient safety the Panel ruled a breach of Clause 4.1 of the Code.

The Panel considered that high standards had not been maintained and a breach of Clause 9.1 of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Proceedings commenced	**29 November 2006**
Case completed	**16 January 2007**

ANONYMOUS v NOVO NORDISK

Employment of diabetes nurses on diabetes helpline

An anonymous 'concerned citizen' alleged that it was unethical for Novo Nordisk to staff its diabetes helpline with nurses who worked in diabetes clinics during the week. The out-of-hours helpline was only for those patients on a Novo Nordisk medicine. Novo Nordisk was thus pressurizing nurses to prescribe its products by paying for a service that let nurses have an extra source of income.

The Panel did not consider it was necessarily unacceptable for Novo Nordisk to employ nurses who worked in diabetic clinics to answer emergency telephone calls to the Novo Nordisk helpline as alleged. Nurses were bound by the Nursing and Midwifery Council Code of Conduct and so they should not allow such employment to influence them when working in the clinic during the day. Nor was it necessarily unacceptable for the helpline to provide emergency support only to patients using Novo Nordisk's products. The Panel ruled that there had been no breach of the Code.

An anonymous 'concerned citizen' complained about the use by Novo Nordisk Limited of diabetes nurses for its diabetes helpline.

COMPLAINT

The complainant noted that Novo Nordisk ran a diabetes helpline which patients taking Novo Nordisk insulin could call for emergency advice after surgery hours during the week and at any time during a weekend. Diabetes nurses were employed to operate the service and answer the telephones but the nurses that Novo Nordisk paid also worked in diabetes clinics during the week. Surely this was unethical and shouldn't be allowed? Novo Nordisk was pressurising diabetes nurses to prescribe Novo Nordisk products by paying for a service that let diabetes nurses have an extra source of income.

The complainant could not believe that a pharmaceutical company was allowed to pay for something that was only for patients on that company's medicine. This must make the nurse want to sell Novo Nordisk products even more!

The complainant requested a full investigation, it was unbelievable that a pharmaceutical company was allowed to carry on in this way.

When writing to Novo Nordisk the Authority asked it to respond in relation to Clauses 2 and 9.1 of the Code.

RESPONSE

Novo Nordisk stated that it employed, on a casual basis, diabetes specialist nurses for the out-of-hours helpline. The purpose of this service was to provide out-of-hours support for people who were currently using Novo Nordisk diabetes products. Patients were encouraged to see their usual health professional as soon as possible after the telephone call, to find a permanent solution to the reason they phoned. The helpline nurses were only to give emergency advice to carry the caller over until the next working day. Nurses with at least three years' experience as a diabetes specialist nurse were selected. They were required to have up-to-date membership with the Nursing and Midwifery Council (NMC) and indemnity cover which was normally provided by the Royal College of Nursing. A record was held by Novo Nordisk of the policies and membership to ensure that these were maintained. The helpline was established in November 2001 after the need for such a service was highlighted by nurses working in the NHS as there was limited out-of-hours support for diabetics. The helpline nurses provided advice on the basis of their clinical knowledge and advice was given in line with generic helpline guidelines. Due to legal reasons, it was not possible to extend this service as standard to cover medicines not manufactured by Novo Nordisk. The helpline was run on the principle that:

- The patients' relationships with their health professional would never be undermined.
- Only the advice necessary to help the patient until the next working day would be given, no changing of prescriptions or longer term interventions would be made. Appropriate information was passed to the patient's health professional on the following working day, with the patient's consent.
- The helpline was not advertised to patients, thereby keeping the health professional in control of the delivery of out-of-hours care.
- Calls not related to a Novo Nordisk product could be answered only with essential emergency advice.
- A nurse would never suggest that a caller changed the products he or she was using.

Advice was recorded and reviewed to ensure that it complied with the ethos of the helpline and was medically sound.

To date no complaints had been received about the service. The feedback from patients who had used this service demonstrated its value in providing reassurance and confidence in an emergency situation.

In April 2004 a registered centre scheme was created in response to requests from hospitals to be kept in the loop of patients' care. Registered centres were sent the helpline feedback forms which were used to record the advice that was given to the patient. There were 82 registered centres which included some of the large centres across the UK all of which had decided to use the helpline to support patients and provide a much needed service.

To date, Novo Nordisk had had no complaints from

registered centres regarding the advice given to callers. The fact that so many diabetes centres had signed up for the registered centre scheme proved it was well respected and valuable.

Novo Nordisk noted that most health professionals working for the NHS also did bona fide work for pharmaceutical companies such as participating in advisory boards, steering committees, speaking at events and writing articles in journals. They received sponsorship for research projects and travel to meetings and conferences and training. Most health professionals would have received bona fide compensation from several pharmaceutical companies over the past year.

While Novo Nordisk did not have any direct control over how nurses behaved within their capacity as NHS nurses, it considered it insulting to suggest that receiving compensation for a few hours' telephone work would influence their prescribing practice.

The Novo Nordisk helpline employed highly experienced and well-respected nurses who abided by the NMC Code of Conduct. They would not compromise their reputation or professional standing by even appearing biased in their practice.

The nurses working on the helpline had very independent views from that of Novo Nordisk and were not afraid to voice their opinion. In the past, Novo Nordisk had had discussions with the nurses working on the helpline where they had not agreed with company decisions, such as the discontinuations of some products.

None of the trusts employing these helpline nurses had objected to them working shifts on the helpline or complained that it changed their usage of Novo Nordisk products. Most decisions about insulin prescribing were made by doctors and not nurses.

PANEL RULING

The Panel did not consider it was necessarily unacceptable for Novo Nordisk to employ nurses who worked in diabetic clinics to answer emergency telephone calls to the Novo Nordisk helpline as alleged. Nurses were bound by the NMC code and so they should not allow such employment to influence them when working in the clinic during the day. Nor was it necessarily unacceptable for the helpline to provide emergency support only to patients using Novo Nordisk's products. The Panel decided that there had been no breach of Clauses 9.1 and 2 and ruled accordingly.

Complaint received **12 December 2006**

Case completed **11 January 2007**

CODE OF PRACTICE REVIEW – FEBRUARY 2007

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1855/6/06	**Novartis v Roche**	**CellCept booklet**	**Two breaches Clause 7.2 Breaches Clauses 7.4, 7.8, 7.10 and 8.1**	**Appeal by respondent**	**Page 3**
1859/6/06	Anonymous Employees v Merck Sharp & Dohme	Medical and educational goods and services	No breach	Appeal by respondent Report from Panel to Appeal Board	Page 15
1862/7/06	**ProStrakan/Director v Shire**	**Breach of undertaking**	**Breaches Clauses 2, 9.1 and 22**	**Appeals by respondent and complainant**	**Page 24**
1870/7/06	**Amgen v Roche**	**Promotion of NeoRecormon**	**Four breaches Clause 7.2 Breaches Clauses 7.3 and 7.4**	**No appeal**	**Page 29**
1871/7/06	**Doctor v Sanofi-Aventis**	**Acomplia journal advertisement**	**Breaches Clauses 3.2, 7.2 and 7.4**	**Appeals by respondent and complainant**	**Page 35**
1876/8/06	**Anonymous Employee v Pfizer**	**Hospital call rates**	**Breach Clause 15.4**	**No appeal**	**Page 43**
1884/8/06	**Hospital Chief Pharmacist v Servier**	**Conduct of Representative**	**Breaches Clauses 9.1, 15.3 and 15.4**	**No appeal**	**Page 46**
1885/8/06 and 1886/8/06	**Roche v Procter & Gamble and Sanofi-Aventis**	**Disparagement of Bonviva**	**Breaches Clauses 7.2 and 8.1**	**No appeal**	**Page 50**
1889/9/06	**Voluntary admission by Servier**	**Conduct of representative**	**Breaches Clauses 9.1, 9.9, 15.2 and 15.9**	**No appeal**	**Page 55**
1890/9/06	**Contract Representative v Servier**	**Representative call rates**	**Breach Clause 15.9**	**No appeal**	**Page 57**
1891/9/06	**Voluntary admission by Lilly**	**Articles in the lay press**	**Breach Clause 20.2**	**No appeal**	**Page 59**
1892/9/06	**Member of the Public v ProStrakan**	**Rectogesic press release**	**Breaches Clauses 9.1 and 20.2**	**Appeal by complainant**	**Page 62**
1894/10/06	**Novartis v AstraZeneca**	**Arimidex mailing**	**Breach Clause 7.2**	**No appeal**	**Page 66**
1896/10/06	Anonymous v Lilly	Alleged inappropriate hospitality	No breach	No appeal	Page 68
1897/10/06	Anonymous v Janssen-Cilag	Alleged inappropriate hospitality	No breach	No appeal	Page 72
1898/10/06 and 1900/10/06	**General Practitioners v Procter & Gamble**	**'Dear Doctor' letter about mesalazine**	**Breach Clause 9.1**	**No appeal**	**Page 74**
1901/10/06	Primary Care Trust Chief Pharmacist/ Associate Director of Public Health v GlaxoSmithKline	'Dear Practice Nurse' letter about Rotarix	No breach	No appeal	Page 77

1906/10/06	**Paragraph 17/Director v Servier**	**Training material**	**Breaches Clauses 2, 9.1 and 15.9**	**No appeal**	**Page 79**
1907/10/06	**Galen v Ivax**	**Promotion of Mucodyne**	**Three breaches Clauses 7.2 Two breaches Clause 7.4 Two breaches Clause 7.10**	**No appeal**	**Page 82**
1908/11/06	**Voluntary Admission by Lilly**	**Arrangements for a meeting**	**Breaches Clauses 9.1 and 19.1**	**No appeal**	**Page 86**
1909/11/06	Medical Representative v AstraZeneca	Arrangements for meetings	No breach	No appeal	Page 88
1916/11/06	Primary Care Trust Head of Medicines Management v Janssen-Cilag	Memory stick as promotional aid	No breach	No appeal	Page 90
1918/11/06	**Voluntary Admission by Amgen**	**Promotion of prescription only medicine to the public**	**Breaches Clauses 15.2 and 20.1**	**No appeal**	**Page 91**
1920/11/06	Insulin Dependent Diabetes Trust v Novo Nordisk	Advertisement in Diabetes Breakthrough	No breach	No appeal	Page 93
1922/11/06	**Voluntary Admission by GlaxoSmithKline**	**Use of out of date prescribing information**	**Breaches Clauses 4.1 and 9.1**	**No appeal**	**Page 94**
1932/12/06	Anonymous v Novo Nordisk	Employment of diabetes nurses on diabetes helpline	No breach	No appeal	Page 96

PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about prescription only medicines made available to the public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend, buy or sell medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the sponsorship of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr William Harbage QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines, or the provision of information to the public, should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall,
London SW1A 2DY
(telephone 020 7930 9677
facsimile 020 7930 4554)
By email to: complaints@pmcpa.org.uk.