PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 58 NOVEMBER 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.

European Federation of Pharmaceutical Industries and Associations - New Codes

On 5 October, the European Federation of Pharmaceutical Industries and Associations (EFPIA) agreed two new codes of practice.

One is the 'EFPIA Code on the promotion of prescription – only medicines, and interactions with, healthcare professionals'. This Code will replace the current 'EFPIA Code on the promotion of medicines' and introduces requirements in a number of new areas: donations and grants that support healthcare or research, fees for service, the use of consultants and non-interventional studies of marketed medicines.

The other is the 'EFPIA Code of Practice on relationships between the pharmaceutical industry and patient organisations'. This a new topic for the EFPIA though it is already dealt with in the ABPI Code of Practice.

Both Codes have to be brought into force by member associations by no later than 1 July 2008. Consideration is currently being given to what changes will be needed to the ABPI Code in order to do this. There will be consultation with companies and others in due course. It is anticipated that a new Code will come before ABPI members at the Annual General Meeting in April.

Public reprimand for AstraZeneca

AstraZeneca has been publicly reprimanded by the Code of Practice Appeal Board for not fully investigating a complaint when it responded to Pfizer and in its first response to the Authority. AstraZeneca had not made sufficient investigations and as a result it had provided incorrect responses which was totally unacceptable. The Appeal Board considered this matter to be of the utmost seriousness. In addition the Appeal Board required an audit of AstraZeneca's procedures.

Full details can be found at page 41 of this issue of the Review in the Report for Case AUTH/1977/3/07.

Arm's length arrangement or not?

It is possible for a company to sponsor material, produced by a third party, which mentions its own products, and not be liable under the Code for its contents, but only if, inter alia, there has been a strictly arm's length arrangement between the parties. In practical terms the arrangements must be such that there can be no possibility that the pharmaceutical company has been able to exert any influence or control over the final content of the material.

Factors which might mean there had not been a strictly arm's length arrangement would include, but not be restricted to:

- Initiation of the material, or the concept for it, by the pharmaceutical company
- Influence from the pharmaceutical company on the content/balance/scope of the material
- Choice/or direct payment of the authors by the pharmaceutical company

Companies should remember that use of material for a promotional purpose will mean that material is subject to the Code.

Do you still need the printed Code of Practice Review?

If you sign up for PMCPA e-alerts on the relaunched website (www.pmcpa.org.uk) you will automatically be alerted by email when the latest issue of the Review is available, so you may no longer need to be sent the printed version.

If, however, you would nonetheless like to continue to receive the printed version, please tell us so by email (lmatthews@pmcpa.org.uk).

Printed copies will continue to be sent to pharmaceutical company chief executives.

Reporting of adverse reactions

Clause 4.10 of the Code states that 'All promotional material, other than promotional aids, must include prominent information about adverse event reporting mechanisms'.

The supplementary information states 'The requirements of this clause can be met by the inclusion of the statement 'Information about adverse event reporting can be found at www.yellowcard.gov.uk' or similar and 'Adverse events should also be reported to [the relevant pharmaceutical company]'. A telephone number for the relevant department of the company may be included. Text is more likely to be deemed to be prominent if it is presented in a larger type size than that used for the prescribing information'.

Many companies are following the suggested wording in their promotional material. The Medicines and Healthcare products Regulatory Agency (MHRA) has raised the topic of reporting of adverse events as part of regular discussions about the Code. It is of course important that adverse events are reported. The MHRA is keen that all companies use the actual wordings in

Continued overleaf

CODE OF PRACTICE TRAINING

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

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

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

Monday, 21 January 2008
Monday, 25 February 2008

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

For further information regarding any of the above, please contact Nora Alexander for details (020 7747 8885 or email nalexander@pmcpa.org.uk).

How to contact the Authority

Our address is:

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

www.pmcpa.org.uk

Telephone: 020 7747 8880
Facsimile: 020 7747 8881

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

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

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

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

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

Reporting of adverse reactions continued

the supplementary information and companies are asked to do so.

Clause 4.10 along with the requirements for black triangles (supplementary information to Clause 4.3) are being considered in the current review of the requirements of the Code.

Goodbye Julie . . .

Julie Gadsby who was with the Authority as Personal Assistant to the Director left earlier this year. The Authority thanks Julie for her hard work on its behalf and wishes her well with her future career.

. . . Hello Nora

The Authority has welcomed Nora Alexander to its staff. Nora has replaced Julie Gadsby and her responsibilities include the organization of the familiarization seminars on the Code of Practice. Nora's telephone number is 020 7747 1443 and her email address is nalexander@pmcpa.org.uk. The Authority looks forward to the positive contribution which Nora will make to its work.

EMPLOYEE v SANOFI-AVENTIS and PROCTER & GAMBLE

Osteoporosis audit programmes

An anonymous complainant, writing under a pseudonym and describing himself as a current employee of Sanofi-Aventis working in the UK, alleged inappropriate service offerings by both his employer and Procter & Gamble. Procter & Gamble and Sanofi-Aventis worked together as the Alliance for Better Bone Health (ABBH) to promote Actonel (risedronate) for the treatment of osteoporosis. The services at issue had been offered by the ABBH when it consisted of Aventis, ie prior to its merger with Sanofi-Synthelabo to become Sanofi-Aventis, and Procter & Gamble.

The complainant provided a number of documents relating to the ABBH sponsored osteoporosis nurse audit programme, delivered by agency nurses, which he alleged showed that the service had been implemented in a fashion that repeatedly and unequivocally linked its provision to product usage. This was totally unacceptable and failed to adhere to both the letter and spirit of the 2003 and 2006 Codes on multiple counts. The programme ran from 2002 until 2004 involving 424 practice based audits. Seemingly, this programme was heralded as a major commercial success within the ABBH having resulted in 17,532 patients being initiated on a bisphosphonate, the vast majority on Actonel.

The complainant alleged that a substantial proportion of the nurse audit programme was concerned with steroid-induced osteoporosis. For much of the time that this programme was implemented, however, Actonel once weekly was not licensed for this indication. Accordingly, in addition to inappropriate linkage of so-called 'service to medicine' to use of the sponsor companies' product, unethical promotion of an unlicensed medicine might have been effectively conducted through this programme. If demonstrated to be true then the latter point would bring further disgrace upon the industry at best and potentially represent a threat to patient safety at worst.

The Panel considered that the complaint concerned both the nurse audit and the associated Osteoporosis Primary Care Audit Tool (TOPCAT) service.

The Panel noted that the nurse audit, which ran from 2002 until 2004, was sponsored by the ABBH which comprised Procter & Gamble and Aventis.

The Panel noted that the material for health professionals referred to the ABBH and bore a declaration of sponsorship which referred to Aventis and Procter & Gamble. Some of the documents provided by the complainant referred to the ABBH.

Case AUTH/1903/10/06 - Procter & Gamble

The Panel noted that Procter & Gamble acknowledged that as far as it was aware the Nurse Audits document supplied by the complainant had been created within Procter & Gamble in May 2004. The document clearly linked the provision of the service to the prescription of Actonel. The objectives included increasing sales by identifying new patients in Actonel friendly surgeries and increasing Actonel new patient share post audit. A section of the document was entitled 'Business Return'; the final two points made in that section were '80% of new o/p patients get Actonel – national figure 25%' and 'Increase in 35mg Actonel share from 6.6% to 26.9%'. Surgeries were nominated for the service if they were 'Actonel friendly'.

The TOPCAT Surgery Nomination Form (provided by the complainant), in a section entitled 'Checklist' also referred to Actonel - one of the checklist statements was 'Surgery preferred bisphosphonate therapy for all licensed indications is Actonel'. Completed forms were to be sent to 'your regional manger copying in ABBH colleagues'. The Panel noted Procter & Gamble's submission that the reference number on this document suggested that it had gone through the copy approval process. A flow chart for selection of TOPCAT surgeries bore an identical reference number and instructed representatives to check first of all 'Is this Surgery First Line?' The TOPCAT Briefing Document, for internal use only, (provided by the complainant) appeared to be aimed at representatives. Procter & Gamble had not commented on this document which stated that the service was for use 'where Actonel is first line'. TOPCAT was designed to complement the nurse audit programme which was described as a major strategic investment for the ABBH. It stated that based on a surgery with 5,000 patients TOPCAT would deliver an average 25 patients suitable for Actonel initiation which translated into an extra £5,200 on yearly sales per practice. It referred to the ABBH, set out a suggested sales story and stated 'representatives of Aventis (and P&G) will not …' be present or involved in certain activities.

The Panel noted Procter & Gamble's submission that it could find no evidence that the Nurse Audits document, or the TOPCAT surgery nomination form, had been supplied to the sales force. The Panel further noted Procter & Gamble's submission that it was highly likely that the Nurse Audits document was only used as a positioning document for head office staff, however the document addressed the

representatives directly, referring to 'your RBM' and summarized the representatives' role beneath the heading 'process'. The Panel queried whether such references were consistent with a head office positioning document.

The Panel noted Procter & Gamble's submission that documents used internally indicated that representatives were encouraged to identify 'Actonel first use surgeries' or 'Actonel friendly surgeries' for the nurse audit programme or TOPCAT and also that representatives should be confident that GPs would be likely to prescribe risedronate before nominating practices for inclusion in the programme. In that regard the company provided a document, Actonel GP Call Agenda and Follow Up – November 02 to January 03, which clearly showed that only when surgeries agreed to prescribe Actonel first choice or first line, were they offered the nurse audit service. A document, Programme: Update and Changes to Osteoporosis Review, was printed on Aventis and Procter & Gamble headed paper and signed by the Actonel team. It stated that assessment of the surgeries already reviewed showed there to be an increased proportion of patients already receiving bisphosphonate treatment compared to the pilot. This reduced the number of patients in each surgery that could benefit from the review. Therefore the quality of nominations needed to improve. The accompanying Sales Force Call Agenda (June 2003) again clearly linked the offer of the service to those practices which agreed to prescribe Actonel first choice.

The Panel noted that having selected practices on the basis that they prescribed Actonel first choice/first line, the documents given to customers in respect of the nurse audit programme and TOPCAT did not refer to Actonel. These documents referred to a selection of treatments; bisphosphonate, SERM and calcium and Vitamin D supplement of choice.

The Panel considered that the internal documents for the nurse audit and for TOPCAT did not meet the requirements of the 2003 Code. The documents were such that representatives would only offer the services to those surgeries that agreed to use Actonel first choice/first line. In that regard the Panel noted that Procter & Gamble had data to show that 88% of all treated patients were initiated on Actonel in the nurse audit programme between March 2003 and October 2004. In 2004 approximately 60 patients were started on Actonel as a result of TOPCAT. The Panel considered that the selection of practices for the nurse audit and TOPCAT was unacceptable; the arrangements were contrary to the requirements of the Code and a breach was ruled. This ruling was appealed.

The Panel further considered that the overall arrangements brought discredit upon the pharmaceutical industry; a breach of Clause 2 was ruled. This ruling was appealed.

The Panel decided to report Procter & Gamble to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the 2006 Constitution and Procedure.

With regard to the promotion of Actonel for corticosteroid-induced osteoporosis, the Panel noted that throughout the period of the nurse audit and of TOPCAT, Actonel 5mg was so licensed. Although Actonel 35mg was not licensed for use in corticosteroid-induced osteoporosis, there was no evidence that it had been promoted for such an indication. No breach was ruled in that regard.

Case AUTH/1902/10/06 - Sanofi-Aventis

The services in question had been run by Aventis prior to its merger with Sanofi. The Panel noted Sanofi-Aventis' submission that none of its current management team had been involved with the nurse audit; no-one from Aventis' medical or regulatory teams had transferred to the new company which had no involvement in the pre-2005 ABBH when the documents at issue were created and used. The Panel considered that Sanofi-Aventis was, nonetheless, responsible for the acts or omissions of Aventis in the past which came within the scope of the Code. Sanofi-Aventis had had to rely on incomplete records archived by Aventis to form its response. Procter & Gamble had provided Sanofi-Aventis with a copy of its response.

The Panel noted Sanofi-Aventis' comments about the logistical and other difficulties associated with the merger. Nonetheless, given Sanofi-Aventis' continuing responsibilities under the Code for acts/omissions of Aventis it was beholden upon companies wherever possible to use their best endeavours to ensure that relevant material and job bags were retained. Sanofi-Aventis should at the very least have been able to produce job bags for the relevant training material from early 2004.

The Panel noted Sanofi-Aventis' submission that it had no archived record of the documents supplied by the complainant ie the Nurse Audits document, the TOPCAT surgery nomination form and the TOPCAT briefing document. (The first document was acknowledged by Procter & Gamble, as far as it was aware, to have been drafted by it. Procter & Gamble acknowledged that the second document appeared to have gone through its certification process. In the Panel's view the TOPCAT briefing document was likely to have gone through Procter & Gamble's certification process given the similarity of its reference code to the reference code on the other two documents.) In its response Sanofi-Aventis submitted documents supplied to customers.

Nonetheless the Panel noted that the Nurse Audits document, the TOPCAT flow chart, the TOPCAT surgery nomination form and TOPCAT briefing document were originally provided by the complainant who described himself as a current employee of Sanofi-Aventis. He corresponded with the Authority under a pseudonym. The Panel was thus extremely cautious when deciding what weight to attribute to this evidence. The provision of relevant documents by a current Sanofi-Aventis

employee might be seen as inconsistent with the company's comments on the availability of documents. Nonetheless the Panel did not know how or from where the complainant had obtained the documents.

The Panel further noted Sanofi-Aventis' submission that the ABBH was a collaboration between two independent companies and that as such it was likely that the two had differing involvement and participation in particular initiatives. The Panel noted, however, that Procter & Gamble had submitted a document (Programme: Update and Changes to Osteoporosis Review) which clearly linked the two companies (it was headed with the two company logos) and which in the accompanying Sales Force Call Agenda (June 2003) clearly linked the provision of the nurse audit service to the prescription of Actonel ie call objective was to gain agreement to prescribe Actonel as first choice. The Sales Force Call Agenda referred to completing the booking form with input from 'local Alliance territory team including opposite Alliance RBM/RSM, P&G Account Executive and Aventis Hospital Rheumatology Team'. Weekly update reports would be sent to 'all Alliance RBM/RSMs including approved nominations tracker…'.

The Panel considered that the Programme: Update and Changes to Osteoporosis Review document did not meet the requirements of the Code. Sanofi-Aventis had been provided with a copy of Procter & Gamble's response by Procter and Gamble. The Authority had asked Sanofi-Aventis to comment on any differences. Sanofi-Aventis had not commented on this specific document. The document encouraged representatives to only offer the service to those surgeries which used Actonel as first choice. The Panel noted its comments above on the TOPCAT documents which referred to the ABBH and to Aventis. The Panel considered that the selection of practices for the nurse audit and TOPCAT was unacceptable; the arrangements were contrary to the requirements of the Code and a breach was ruled. This ruling was appealed.

The Panel further considered that the overall arrangements brought discredit upon the pharmaceutical industry; a breach of Clause 2 was ruled. This ruling was appealed.

The Panel decided to report Sanofi-Aventis to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the 2006 Constitution and Procedure.

With regard to the promotion of Actonel for corticosteroid-induced osteoporosis, the Panel noted that throughout the period of the nurse audit and of TOPCAT, Actonel 5mg was so licensed. Although Actonel 35mg was not licensed for use in corticosteroid-induced osteoporosis, there was no evidence that it had been promoted for such an indication. No breach was ruled in that regard.

Upon appeal in Cases AUTH/1902/10/06 and AUTH/1903/10/06, the Appeal Board noted that osteoporosis was a serious disease and that a service which would increase diagnosis and treatment would be of benefit to patients. Nonetheless any such service had to comply with the Code.

The Appeal Board was concerned about the limited documentation provided by the companies and noted their explanations in this regard. In relation to the material provided by the complainant the Appeal Board noted that whilst it was possible to contact the complainant his identity was unknown and thus it was extremely cautious when deciding what weight, if any to attach to his evidence.

The Appeal Board noted that the parties' submissions differed. Nonetheless there were some similarities between them. The complainant had provided documents which he stated were intended to be used by representatives; the companies disagreed and stated that the documents had not been used in the field. The Appeal Board ultimately concentrated on two documents regarding the nurse audit which both companies agreed had been used by sales personnel; a document headed 'Actonel GP Call Agenda and Follow Up November 02 to January 03' and the Sales Force Call Agenda (June 2003) document.

The 'Actonel GP Call Agenda and Follow Up' appeared to set out the sequence of events from a sales call to an audit call. The first instruction was 'Call objective 1: Gain agreement to Rx Actonel as 1st choice therapy for patients with low BMD [bone mineral density], [corticosteroid induced osteoporosis], patients with previous fragility fracture'. If the call objective was not achieved then representatives were given a second call objective of 'If dosing were not an issue Gain agreement to proactively Rx Actonel 1st line for [the same group of patients]'. If the answer was still no then representatives were to do the second product detail. Conversely if call objective 1 or 2 was achieved the next step was referred to as Step 1 of the Audit call which was to 'Book another appointment with the GP with a profile objective: To gain a full understanding of GP's level of interest and commitment to conducting an osteoporosis review in the practice … WITHOUT ACTUALLY OFFERING THE [nurse audit] SERVICE'. Having done that the representative then had to book an appointment with the most influential GPs in the practice to ensure that they supported an osteoporosis review. The Appeal Board considered that the document was in effect briefing material which instructed representatives how to offer the service. It appeared that representatives would not offer the service until they were sure that the doctors in the practice supported an osteoporosis review and would, as part of that review, prescribe Actonel as either first choice or first line therapy to suitable patients. The Sales Force Call Agenda (June 2003) similarly showed that a doctor's agreement to prescribe Actonel as first choice therapy was the first hurdle to being offered the service. This document also included an assessment of suitability for osteoporosis review which included a cut off of a total patient population above 3,000 for the audit service to be offered.

The Appeal Board considered that companies had to be clear and unambiguous when instructing representatives about their role in such matters. The Appeal Board considered that the link between the promotion of Actonel and the provision of the service including the selection of practices as described in the material was unacceptable. The Appeal Board did not accept the companies' submission that the two documents clearly separated the sales and non promotional call. The Appeal Board considered that neither the content or layout of either document were satisfactory in this regard. The companies' representatives acknowledged that the layout of the documents was 'unfortunate'.

As an indication as to how the service was offered in practice, the Appeal Board noted that a statement from one of Procter & Gamble's employees read 'If a particular doctor indicated that, where a bisphosphonate was indicated, he would only prescribe a product manufactured by one of our competitors (eg Fosamax) and would not consider risedronate [Actonel], then representatives would not routinely book a second appointment to discuss the Nurse Audit Programme. Nevertheless, this does not mean that practices who did not prescribe risedronate were excluded and some such practices did, in fact, participate in the Programme'.

Notwithstanding the statement that some surgeries which did not prescribe Actonel were offered the service, the Appeal Board considered that the link in the representatives' material between the promised prescription of Actonel by the doctor and the subsequent offer of the service by the representative was unacceptable. It considered that the criteria for the selection of practices and the failure to adequately separate the promotional and non promotional role of the representatives was such that the arrangements failed to comply with the Code. The Appeal Board upheld the Panel's ruling of a breach. The Appeal Board considered that the concerns about the material which gave rise to the breach were so serious that they brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2.

The Appeal Board noted its comments above about the weight to be attached to the evidence. The Appeal Board considered that there was insufficient evidence to establish, on the balance of probabilities, whether the arrangements for the TOPCAT service complied with the Code. The Panel's ruling in this regard no longer stood. Accordingly, there was no breach of the Code in relation to arrangements for the TOPCAT service.

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 breaches of the Code in relation to the nurse audit programme. The Appeal Board was concerned about the paucity of documentation provided by both companies. The Appeal Board decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require an audit of both companies' procedures in relation to the Code to include an examination of policies and procedures relating to the ABBH. On receipt of the audit reports the Appeal Board would decide if any further action was required.

Upon receipt of the audit report of Sanofi-Aventis, the Appeal Board decided that on the basis that the recommendations were implemented no further action was required.

The Appeal Board considered that the audit report of Procter & Gamble showed that there was much work still to be completed to implement the recommendations and it was concerned about the inadequacy of the certification arrangements. The Appeal Board decided that Procter & Gamble should be re-audited in January 2008.

An anonymous complainant, writing under a pseudonym and describing himself as a current employee of Sanofi-Aventis working in the UK, complained about alleged inappropriate service offerings by both his employer and Procter & Gamble Pharmaceuticals UK Limited. Procter & Gamble and Sanofi-Aventis worked together as the Alliance for Better Bone Health (ABBH) to promote Actonel (risedronate) for the treatment of osteoporosis. The complaint was taken up with both companies. The services at issue had been offered by the ABBH when it consisted of Aventis ie prior to its merger with Sanofi Synthelabo to become Sanofi-Aventis, and Procter & Gamble.

COMPLAINT

The complainant provided a number of documents relating to the ABBH sponsored osteoporosis nurse audit programme, delivered by agency nurses, which he alleged showed that the service had been implemented in a fashion that repeatedly and unequivocally linked its provision to product usage. This was totally unacceptable and failed to adhere to both the letter and spirit of the 2003 and 2006 Codes on multiple counts. The complainant deplored and was profoundly concerned to see an organisation which he had held in very high regard engaged in such unethical marketing practices on a grand scale. The programme ran from 2002 until 2004 involving 424 practice based audits. Seemingly, this programme was heralded as a major commercial success within the ABBH having resulted in 17,532 patients being initiated on a bisphosphonate, the vast majority on Actonel.

If the pharmaceutical industry was to ever enjoy the confidence of the government and the public it must strive to permanently eliminate such unethical practices. The current case involved the ABPI President's company and was therefore likely to seriously undermine confidence in the industry's ability to self-regulate. The complainant, like many colleagues in the UK pharmaceutical industry, wanted to look forward to a long and fulfilling career in the industry but he viewed recurrences of unethical practices as a major threat to that goal and would not

tolerate the malpractice of others impacting on his ability to make a living in a business to which he was completely committed. Accordingly, he requested that the Authority fast-track the current case; if necessary an emergency meeting of the ABPI Board of Management could be called within the next week. The complainant wanted to provide the industry with the opportunity to self-regulate its way out of another self-inflicted crisis. However, failure to take appropriate corrective action within four weeks of receipt of this letter ie by end-of-business on Friday, 17 November 2006, would result in alternative avenues being pursued to rectify the current ethical crisis evident across the business. The Medicines and Healthcare products Regulatory Agency (MHRA) would be the next port of call; in the unlikely event that the national regulator chose not to act rapidly on this matter then the complainant would see no alternative but to place this information in the public domain and allow the media to determine the industry's fate. The industry's reputation was clearly at its lowest ebb and so now was as good a time as any to bring the skeletons from the closet, face the music and change its ways for good.

Like many of his colleagues, the complainant felt that the UK pharmaceutical industry was sitting on a precipice in respect of its likelihood of maintaining the privilege to self-regulate its business practices. Decisive action must be taken against those who would endanger self-regulation for the consequences of the introduction of a body such as the Financial Services Authority in the industry's sphere of business would be catastrophic for its collective reputations and make day-to-day business far more cumbersome than was currently the case.

He appealed to the Authority to act decisively and fast in the matter of the ABBH osteoporosis nurse audit program.

In subsequent correspondence the complainant alleged that a substantial proportion of the nurse audit programme was concerned with steroid-induced osteoporosis. For much of the time that this programme was implemented Actonel once weekly was not licensed for this indication. Accordingly, in addition to inappropriate linkage of so-called 'service to medicine' to use of the sponsor companies' product, unethical promotion of an unlicensed medicine might have been effectively conducted through this programme. If demonstrated to be true then the latter point would bring further disgrace upon the industry at best and potentially represent a threat to patient safety at worst.

When writing to the companies, the Authority asked them to respond in relation to Clauses 2, 3.1 and 18.1 of the Code.

Case AUTH/1902/10/06 - Sanofi-Aventis

RESPONSE

Sanofi-Aventis stated that the nurse audit ran from 2002 until 2004 and was sponsored on behalf of the original ABBH members Procter & Gamble and Aventis UK. The complainant had also submitted materials which related to an associated service the osteoporosis primary care audit tool (TOPCAT).

Sanofi-Aventis was surprised at the language and content of some of these materials.

However, the programme subject to this complaint was not in existence, and had not been conducted during the tenure of the current management team of Sanofi-Aventis. The programme services were discontinued before the acquisition in December 2004 of Aventis by Sanofi.

The new Sanofi-Aventis team managed the combined operations of Sanofi and Aventis in the UK from the first quarter of 2005. Sanofi-Aventis introduced new management teams and implemented new procedures and certifying signatories.

Aventis was formed in 1999 after the merger of Rhone Poulenc Rorer and Hoechst Marion Roussel. Aventis' operational activities were based at its UK headquarters in Kent until December 2004, after which the site was closed except for IT support and postal redirection. Aventis documentation was archived without moving to the Sanofi-Aventis head-office.

The current ABBH members and their management had therefore relied on documentation archived by previous ABBH members to respond to this complaint.

Sanofi-Aventis would address key facts before responding to the allegations.

Relevant service providers

A third party nurse advisor audit support service and a third party data processing service were used.

No members of the Aventis medical or regulatory teams transferred to Sanofi's business. There was therefore virtually no transfer of know-how or of history to Sanofi. Sanofi standard operating procedures (SOPs) were implemented throughout the new operations in the first quarter of 2005.

ABBH

The ABBH was set up in 1997 in the US, and then in the UK by Procter & Gamble and Hoechst Marion Roussel, which on its merger in 1999 with Rhone Poulenc Rorer became Aventis, to share know-how and certain costs (salesforce, promotional and non-promotional services) relating to the marketing of Actonel 5mg once daily and 35mg once weekly. It was not a separate legal entity nor a co-promotion nor a joint venture. The key competitors were Fosamax once weekly, then alendronate once daily and once weekly. Evidence of the market share of osteoporosis treatments could be found in the National Institute for Health and Clinical Excellence (NICE) Technology Appraisal No 87.

Overview of documents and services

Sanofi-Aventis had found documents pertaining to an ABBH nurse audit programme and the TOPCAT service. These were certified by the signatories of the historical ABBH members, Aventis and Procter & Gamble and a copy was provided.

Sanofi-Aventis had no archived record of the documents submitted by the complainant and in particular the Nurse Audits document (ref CP&S UK MDO), the TOPCAT Surgery Nomination Form (ref ACT 7330504) and the TOPCAT Briefing Document (ref ACT 8070904). Sanofi-Aventis had been unable to ascertain the origin or creator of these documents for the reasons explained above.

Nurse Audit Programme

Sanofi-Aventis provided copies of the 2002 versions of the Osteoporosis Review Document and the Osteoporosis Review Consent Documentation in order to demonstrate the context of implementation of the services. The company submitted that the audit programme followed a detailed protocol which incorporated best practice guidelines by two different case selection methods. The first identified patients with osteoporosis and/or with a high risk of fracture or further fracture who qualified for immediate treatment. The second included patients with osteoporosis risk factors, but with an unconfirmed diagnosis, warranting a scan to establish appropriate management. The criteria for patient identification were based on the Royal College of Physicians (RCP) guidelines and agreed with the practice.

Informed consent was obtained from the patients. Identified patients had the necessary information relevant for the management of osteoporosis captured and, on completion, these data were presented to the practice. The GP then invited appropriate patients for consultation at the practice using the services of the nurse team. A scan (provided as part of the service) was offered to confirm the diagnosis of osteoporosis in those patients where the information from the scan would alter management or be clinically indicated.

All management or treatment decisions were based on protocols following best practice and approved by the patient's doctor. Given the menu of treatment options, the decision analysis as to the appropriate treatment or management lay with the patient's doctor.

It appeared that representatives could discuss the service in a non-promotional call with practices which would then be prepared to be nominated practices; however, GPs interested in the audit service could also approach the nurses independently. The service was therefore provided primarily to practices which were existing prescribers of Actonel, or to new prescribers of Actonel only in compliance with RCP guidelines and later NICE guidelines, but also to prescribers of other treatments including calcium who requested the services.

The nurse audit appeared to have commenced as a pilot service in late 2001 and was discontinued effective 31 October 2004.

TOPCAT

Sanofi-Aventis provided a 2004 copy of TOPCAT, a patient care tool to help a practice identify patients by using software which screened Read and Drug Codes. Those patients' identified management was reviewed and amended according to the GP's wishes and based on best practice and NICE guidelines. Sanofi-Aventis did not know when the TOPCAT service was discontinued.

Briefing materials to representatives and to the nurse advisor audit service

Aventis representatives were trained on line. For example, Sanofi-Aventis had found 2004 records which demonstrated how Aventis provided training and briefing. It appeared Procter & Gamble briefed the nurse advisor service.

The provision and offer of both the audit service and TOPCAT service would have been subject to the requirements of Clause 18.1 'Provision of Medical and Educational Goods and Services' of the 2001 and 2003 Codes.

Clause 18.1

The nurse advisor audit and TOPCAT services were designed to enhance patient care or benefit the NHS as outlined in the programme overviews. From archived documents Sanofi-Aventis had found no evidence that the services were directly linked to product usage. In verifying the complainant's allegations, Sanofi-Aventis contacted prescribers for their views and one opinion was provided.

In 'Our Healthier Nation', the Secretary of State for Health highlighted the role of osteoporosis in causing fractures in older people noting that, as a result of this disease, falls were a major cause of death and disability. Osteoporosis prevention was therefore included as one the measures recommended to help achieve a 20% reduction in fractures by 2010.

The osteoporosis review incorporated guidance from various osteoporosis guidelines (best practice). In addition the material recognised that each individual practice or local health authority might already have its own policies in place. In summary these audits appeared to have been appropriate services based on sound rationale, designed for the benefit of patients under the full control and discretion of prescribers.

With regard to the supplementary information to Clause 18.1, Sanofi-Aventis noted the following: The services provided to GP practices (review of records to identify patients at risk of osteoporosis without disclosure of confidential information and in accordance with GP's instructions) were performed by teams of qualified nurses, who held full Nursing and Midwifery Council (NMC) accreditation and who had received specialist training in clinical audit and the

needs of osteoporotic patients. These nurses were employed by a third party, not by Procter & Gamble or Aventis (paragraph 1 (i-iv)).

Furthermore it appeared patient safety was not compromised: NICE guidelines which recommended alendronate, etidronate and risedronate as first line treatment options were followed; clear protocols were drawn up which gave prescribers unrestricted treatment options. It appeared that representatives provided information about the service in non-promotional calls and forwarded the names of interested practices to the independent service providers.

The audit programme conformed to the requirements of the General Medical Council (GMC) Guidelines, Data Protection Act 1998 and the Caldicott Principles to ensure patient confidentiality (paragraph 1 (v)).

The independent nurses were registered and their role complied with the NMC Code of Professional Conduct (paragraph 1 (vi)).

It appeared that the remuneration of the independent nurses was not linked to sales (paragraph 2).

The services conformed to the Data Protection Act 1998. Any clinical data, which might have been collected for research purposes, were anonymised. It appeared the programme sponsors received monthly reports of data, anonymised so that individual patients could not be identified. The written consent of the patient's doctor for the provision of the service in accordance with doctor's instructions was always obtained prior to commencement of the service (paragraph 3).

The audit complied with the terms of an approved protocol, protocol documents and consent forms (paragraph 4).

The independent nurses followed a protocol when introducing themselves to the interested practice, which included transparency regarding the identity of the sponsors (paragraph 5).

The protocol documents clearly outlined the service in detail and were explicit about the sponsors' identity. Data collection and analysis followed a strict protocol. Data were collected using the practice computer and patients' notes. The information was recorded in a register which was left with the practice at the end of the review. The report included all the data and information collated from the patient register and clinical reviews conducted by the independent nurse advisor. In addition, general observations along with any specific practice recommendations in line with existing guidelines for the management of osteoporosis were compiled (paragraph 6).

All the materials were disease orientated and hence consistent with the principles of audit as service to medicine. They were non-promotional, aligned to the current treatment guidelines and did not mention any specific products. The identity of the sponsors was clear in all aspects of the programme (paragraph 7).

Materials relating to the service were examined by the then certifying signatories of the historical ABBH (paragraph 8).

The audit service was a net contributor to the budget of a primary care trust (PCT). This was achieved indirectly through cost savings on fracture related treatment and screening. The biggest bottle-neck to diagnosis and treatment was scanning which was also costly. As part of the audit service a mobile scanning service was made available (paragraph 9).

In its guidance, the GMC advised doctors that 'you must act in your patients' best interests when making referrals and providing or arranging treatment or care'. The audit service, in its design and conduct, increased a clinician's capacity to manage osteoporosis and enhanced patient care and improved quality of life.

Clause 3.1

The protocol followed best practice guidelines and left all treatment and management decisions to prescribing doctors. Sanofi-Aventis had no evidence that the service promoted any of the medicines used for the management of osteoporosis outside their licensed indications.

As regards the allegation that Actonel 35mg was promoted outside of its licensed indications between 2002 and 2004 it was clear that Actonel 5mg od was licensed throughout this time for corticosteroid-induced osteoporosis and that Actonel 35mg once a week was approved in January 2003 for postmenopausal osteoporosis (PMO).

The decision to prescribe any medication, whether Actonel or any other treatment, was entirely that of the GP who approved use of the services.

Clause 2

From documents available to Sanofi-Aventis, it appeared that the services were provided as a service to medicine, designed and implemented to address an important need of practices, for the benefit of patients. It appeared that certified documents demonstrated how under the 2001 and 2003 Codes the services had not brought discredit to the industry and appeared to have generated positive feedback from GPs.

The services were moreover provided by the historical ABBH members which had different management and processes.

Conclusion

Applying the requirement of the 2001 and 2003 Codes, the documents available to Sanofi-Aventis showed that service provision was not directly linked to product usage and complied with applicable guidelines and best practice.

The services were sponsored by the historical ABBH

members between 2002 and 2004. The management and signatories of Sanofi-Aventis had no involvement, influence or other participation in those activities, and had no control over the conduct of the activities or of the archiving of materials or records.

In response to a request for further information Sanofi-Aventis explained that it had reviewed any paper and electronic records it could find and asked Procter & Gamble to search its own records. The logistical difficulties facing the newly merged company were that paper records located at the Aventis headquarters in Kent, if they were retained, were significantly incomplete and archiving records were also incomplete.

It was up to each former Aventis business unit director as to whether electronic records were saved. As none of the former Aventis medical, regulatory, legal or quality control employees who worked on Actonel in 2004 transferred to Sanofi-Aventis in Guildford, there was no formal transfer of electronic records.

As Sanofi-Aventis did not know which records existed before the integration, it could not ascertain whether records had been transferred, archived or destroyed. Furthermore, changes to e-mail and representative's software caused laptop drives to be cleared and replaced with new software in the first quarter of 2005. Sanofi-Aventis was thus entirely reliant on paper or electronic records which might have been informally provided to individual staff of Sanofi during the transition to Guildford, and on documents which appeared, on an inconsistent basis, to have been retained (for example in legal records). Unsurprisingly, most such documents transferred to Guildford appeared to have been created in 2004.

Sanofi-Aventis was thus required to try to understand from those few documents available to it and Procter & Gamble, often out of context, the facts as well as the background to the documents themselves. However, it was clear that Sanofi-Aventis, formed in 2005, would have had no control over the creation, the use or the archiving of documents created and used before that time, and had no involvement in the pre-2005 ABBH when these documents were created or used.

In response to a request for comments on the fact that Procter & Gamble's response was different to that of Sanofi-Aventis, Sanofi-Aventis explained that the ABBH was and continued to be a collaboration between two independent companies. It was therefore likely that the two companies had differing involvement and participation in particular initiatives relating to Actonel.

The ABBH was first constituted in 1997 as an agreement between Hoechst Marion Roussel and Procter & Gamble in the US. After the merger of Hoechst Marion Roussel and Rhone Poulenc Rorer in 1997, to form Aventis, the alliance was extended to other countries. Procter & Gamble had developed Actonel and launched it in the UK in May 2000. Other than the worldwide 1997 agreement, there was no detailed agreement between Aventis and Procter & Gamble relating to the UK ABBH. From anecdotal evidence Sanofi-Aventis understood that Procter & Gamble and Hoechst Marion Roussel, which became Aventis, shared certain marketing costs, and met on a monthly basis to discuss marketing initiatives and review Actonel sales. There were however no common resources (for example salesforce representatives), offices or computer networks. Each company had its own SOPs regarding certification and sign-off of materials.

Sanofi-Aventis could not comment upon the actions of Procter & Gamble relating to Actonel and the programme, its documents or internal procedures. Procter & Gamble had confirmed that it accepted only a breach of Clause 14.1 of the 2003 Code, having regard to the inconsistency of certification of internal briefing materials intended for use with its own representatives (not with Aventis representatives) in the course of offering the programme.

Sanofi-Aventis stated that after an extensive investigation of documents which had become available to it and Procter & Gamble, it had no evidence to indicate that Aventis' involvement in the programme was in breach of the Code.

Sanofi-Aventis noted that the complaint related to events which had occurred between 2002 and 2004, prior to the acquisition of Aventis by Sanofi, which was concluded in December 2004. At these material times, the current activities and management of Sanofi-Aventis did not exist and could therefore have had no knowledge of, or control or involvement in pre-2005 matters. Moreover, Sanofi's and Aventis' pre- and post-2005 operations were conducted using separate legal entities: Sanofi from Sanofi-Synthelabo Limited, whereas Aventis traded out of various companies including Fisons Limited, May & Baker Limited and Aventis Pharma Limited.

Although Sanofi-Aventis had no evidence to suggest any breach of the Code by Aventis it also did not believe that it would be appropriate for any other company to be asked to accept responsibility for activities undertaken historically by Aventis.

Sanofi-Aventis reiterated that Aventis and Procter & Gamble appeared to have each retained and used their own SOPs.

The relevant Aventis SOP, 'Communication Material Approval', was effective from November 2003, and reviewed in November 2004. Although it referred to a Communication Material Central Database, no such database had been mentioned by any former Aventis director and none had been found or transferred to Sanofi-Aventis.

Procter & Gamble and Sanofi-Aventis had also found a pro-forma Actonel Alliance Copy Approval Form dating about 2003. There was no detailed ABBH SOP associated with the use of the forms. It therefore appeared from the form headings that the pre-2005 ABBH members jointly reviewed promotional and non-promotional materials intended for use with third

parties. Sanofi-Aventis did not know if there was any joint review of internal training or briefing materials – anecdotal evidence suggested that the two companies reviewed their own internal communications.

Sanofi-Aventis explained that, as with any corporate reorganisation, the acquisition of Aventis by Sanofi was associated with substantial upheaval and the possibility that relevant Aventis documents were misplaced during that time. Sanofi-Aventis could thus not comment on the potential involvement of Aventis in relation to hypothetical material, which Sanofi-Aventis had not seen.

Sanofi-Aventis also did not believe it would be appropriate for another company to be asked to accept responsibility for such documents when it had no control, involvement or knowledge of them. No manager or signatory of Sanofi-Aventis had been able to review such documents before their use.

Sanofi-Aventis submitted that none of the documents currently available to Sanofi-Aventis supported the complainant's allegations or indicated any breach of the Code on the part of Aventis.

Case AUTH/1903/10/06 - Procter & Gamble

RESPONSE

Procter & Gamble stated that it and Sanofi-Aventis currently collaborated in the marketing of Actonel as the ABBH. The ABBH was formed in 1997; during the life of the Alliance Procter & Gamble's partners had changed in accordance with the company history of Sanofi-Aventis. Procter & Gamble management and other personnel had changed during this period. At the time of the nurse audit programme, Procter & Gamble's partner was Aventis. The ABBH sponsored the osteoporosis nurse audit programme between 2002 and 2004. At the same time the ABBH also sponsored a pilot form of an associated audit tool, TOPCAT.

In 'Our Healthier Nation', the Secretary of State for Health highlighted the role of osteoporosis in causing fractures in older people noting that, as a result of this disease, falls were a major cause of death and disability. Osteoporosis prevention was therefore included as one of the measures recommended to help achieve a 20% reduction in fractures by 2010. The services were thus designed to enhance patient care or benefit the NHS.

After a thorough review of materials, Procter & Gamble appreciated that some of its actions infringed the 2001 and 2003 Codes. It apologised for these past actions, and had taken the appropriate steps to ensure they did not occur again. New policies and procedures had been put in place since these programmes were initiated so as to prevent these types of errors in the future.

Description of audit programmes

Nurse Audit Programme

Procter & Gamble explained that this audit programme ran from July 2002 to November 2004 and followed a detailed protocol which incorporated best practice guidelines, adapted to the needs of individual GP practices. Patients at risk of osteoporosis were identified in surgeries by trained nurses using two different case selection methods. The first identified patients with osteoporosis and/or with a high risk of fracture or further fracture who qualified for immediate treatment. The second included patients with osteoporosis risk factors, but with an unconfirmed diagnosis, warranting scanning to establish appropriate management. The criteria for patient identification were based on the RCP guidelines, and agreed with the practice.

Informed consent was obtained from all patients. Patient information relevant for the management of osteoporosis was captured and these data were presented to the practice. The GP then invited appropriate patients for consultation at the practice using the services of the nurse team. A scan (provided as part of service) was offered to confirm the diagnosis of osteoporosis in those patients where the information from the scan would alter management or be clinically indicated. All management or treatment decisions were based on protocols following best practice and approved by the patient's doctor. The decision on the appropriate treatment or management lay with the patient's doctor.

ABBH representatives promoting Actonel could nominate practices for involvement in the audit programme via a non selling call.

TOPCAT

TOPCAT was initiated as a pilot programme in May 2004. This was a comprehensive electronic audit patient care tool, designed to help a practice identify patients by using software which screened Read and Drug Codes.

The software was mailed to the surgeries, which ran the software through their patient records to identify patients who might benefit from osteoporosis therapy. The clinical management of identified patients was reviewed and amended if appropriate according to the wishes of the GP and based on best practice. Additional features of the programme included guidance on how practices could improve their performance consistent with specific indicators included in the new General Medical Services (GMS) contract and Quality and Outcomes Framework. The service also included disease information for patients.

ABBH representatives promoting Actonel could nominate practices for use of the TOPCAT audit tool via a non selling call.

Roles of each party

The ABBH developed the materials for the programmes and paid for the nurses. Materials used externally were prepared and approved for use by both companies. Representatives from the two companies identified surgeries for inclusion in the programmes.

The two members of the ABBH jointly agreed the programmes and assigned leadership across the ABBH for different aspects of the work.

In the case of TOPCAT, the programme was agreed by both companies, and executed by Procter & Gamble. A CD-ROM was distributed by a third-party supplier to GP practices for use in practice computer systems to identify potential osteoporotic patients. Data from the programme was analysed by the third party.

Process by which surgeries were selected

Representatives nominated surgeries for inclusion in the audit programme if: there was more than one GP in the practice; the practice had a patient population above 3000; no osteoporosis related review had been conducted in the last 2 years; more than 20% of the patients in the surgery were >60 years of age; all practice partners agreed to having practice records searched by the nurse and GPs in the practice were known to prescribe Actonel for use in osteoporosis.

In the case of TOPCAT, surgeries were nominated to receive access to the audit tool if: they were not suitable for the nurse audit programme nomination (too few patients); no osteoporosis audit had been conducted within last 3 years; the practice agreed to initiate treatment once patient records were audited; the service was compatible with surgery records management systems and GPs in the practice were known to prescribe Actonel for use in osteoporosis.

Process by which treatment was initiated

The nurse identified patients who might benefit from therapy for osteoporosis. The physician then determined the best treatment for the patient.

In the case of TOPCAT, the programme allowed a particular surgery to manage patients in a variety of ways. One option was for the system to generate a letter which invited the patient into the surgery for a consultation, at which time the doctor would decide the most appropriate treatment. An alternative was for the system to generate a letter to which the doctor could attach a prescription to send to the patient. The option to be followed was determined by the individual doctor.

Percentage of patients initiated on Actonel

From data provided from the nurse audit programme, from March 2003 to October 2004, 351 practices were audited, involving 2,203,612 patients. 28,280 patients were invited for screening by their GPs, of which 16,759 were treated with any therapy. 15,046 (53%) of screened patients were treated with Actonel (88% of all treated patients).

From the TOPCAT programme, 72 practices were nominated for use of this audit tool in 2004, involving 272,322 patients. 2,956 patients were identified as being at risk of osteoporosis. Approximately 60 patients were initiated on Actonel therapy in this timeframe.

For perspective, approximately 163,000 patients were treated with Actonel from March 2003 to October 2004. The NICE Guidelines 2005 stated that in 2003/4, the market share for Actonel was 16% of bisphosphonate prescriptions in England. Alendronate market share was 61%, and etidronate market share was 23%.

Documents relating to the programmes

Procter & Gamble had searched its records for the two documents provided by the complainant. Procter & Gamble did not systematically archive electronic messages, however, the Nurse Audits document (ref CP&S UK MDO), had been found in an electronic archive saved as 'details of nurse programme', and dated from 7 May 2004. As far as Procter & Gamble could establish, this document was drafted within Procter & Gamble for internal head office use, and was not circulated to any sales representatives.

The reference number of the TOPCAT Surgery Nomination Form (ACT 7330504) suggested it went through the official Procter & Gamble copy approval process. This had been discovered as an electronic file, however, this had not been found in Procter & Gamble's archives of certified materials. It was possible that this was destroyed in a fire at the Procter & Gamble off-site storage facility in July 2006. Neither Procter & Gamble nor Sanofi-Aventis could find anything to indicate that this specific version of the document was deployed to the sales force in either company.

Clause 18.1

The nurse audit and TOPCAT services were designed to enhance patient care or benefit the NHS as outlined in the programme overviews. The programme incorporated guidance from various osteoporosis best practice guidelines. In addition the programme materials recognised that each individual practice or health authority might already have its own policies. In summary, the ABBH believed these audits were appropriate services based on sound rationale designed for the benefit of patients under the full control and discretion of prescribers.

With regard to the supplementary information to Clause 18.1, Procter & Gamble noted the following: the services provided to GP practices (review of records to identify patients at risk of osteoporosis without disclosure of confidential information and in accordance with GP's instructions) were performed by teams of qualified nurses, who held full NMC accreditation and who had received specialist training in clinical audit and the needs of osteoporotic patients. These nurses were employed by a third party, not by Procter & Gamble or Aventis. No product name appeared on external materials used in the programme, and materials were clearly marked as being sponsored by the ABBH. The sales representatives involved in recruiting practices into the programme carried out two separate calls. One was an Actonel sales call and the second an 'Osteoporosis Review Call'. The second call was devoted to determining if GPs would be interested in becoming involved in the programme and did not involve any promotion (paragraph 1 (i-iv)).

The audit programmes conformed to the requirements of the GMC Guidelines, Data Protection Act 1998 and The Caldicott Principles to ensure patient confidentiality. Neither the ABBH nor its representatives had access to any information that could be linked to particular patients (paragraph 1 (v)).

The independent nurses were registered and their role complied with the NMC Code of Professional Conduct (paragraph 1 (vi)).

The remuneration of the independent nurses was not linked to sales (paragraph 2).

The services conformed to the Data Protection Act 1998. Any clinical data, which might have been collected for research purposes, were anonymised. The programme sponsors received anonymised monthly reports of data, such that neither individual patients nor GPs could be identified. The written consent of the patient's doctor for the provision of the service in accordance with doctor's instructions was always obtained prior to commencement of the service (paragraph 3).

The audit complied with the terms of an approved protocol, protocol documents and consent forms (paragraph 4).

The independent nurses followed a protocol when introducing themselves to the interested practice, which included transparency regarding the identity of the sponsors (paragraph 5).

The protocol documents clearly outlined the service in detail and were explicit about the sponsors' identity. Data collection and analysis followed a strict protocol. Data were collected using the practice computer and patients' notes. The information was recorded in a register which was left with the practice at the end of the review. The report included all the data and information collated from the patient register and clinical reviews conducted by the independent nurse advisor. In addition, general observations along with any specific practice recommendations in line with existing guidelines for the management of osteoporosis were compiled. If the practice requested, a presentation of the findings was made (paragraph 6).

All the materials provided to the nurses and GPs were disease orientated and hence consistent with the principles of audit as a service to medicine. They were non-promotional, aligned to the current treatment guidelines and did not mention any specific products. The identity of the sponsors was clear in all aspects of the programme (paragraph 7).

Materials relating to the service provided to the GPs were examined by the certifying signatories of the ABBH (paragraph 8).

The audit service was a net contributor to the budget of a PCT. This was achieved indirectly, through cost savings on fracture related treatment and screening. The biggest bottle-neck to diagnosis and treatment was scanning which was also costly. As part of the audit service a mobile scanning service was made available. In its guidance, the GMC advised doctors that 'you must act in your patients' best interests when making referrals and providing or arranging treatment or care' (paragraph 9).

The services were not designed by the ABBH as an inducement to prescribe Actonel. Company personnel involvement extended to nominating practices for the service. All documents provided to GPs were reviewed and approved via the ABBH-agreed copy approval system and complied fully with the 2001 and 2003 Codes. These documents did not suggest that the services might not be offered to practices unless Actonel prescribing would result and hence the GP was not led to believe that he could not participate in the programme unless he prescribed Actonel. This supported the ABBH position that the provision of the service to individual GPs was not an inducement to the doctor to prescribe Actonel.

There was no evidence that practices who wanted to participate in the programme were excluded from this audit service because of a requirement relating to their prescription intent. Furthermore, given the NICE guidance which recommended alendronate, etidronate and Actonel as first line treatment options it was inconceivable that the nomination of 'Actonel friendly' practices would compromise choice given the well established treatment guidelines, the clear protocols as part of the audit service and the market leadership of alendronate.

Although none of the information provided to the GPs could be considered to represent an inducement to prescribe, it was recognised that internal documents encouraged representatives to identify 'Actonel first line surgeries' or 'Actonel friendly surgeries' for inclusion in the audit programmes. The documents also indicated that representatives should be confident that GPs would likely prescribe Actonel before nominating practices for inclusion in the programme.

Procter & Gamble acknowledged that the use of some of the internal documents associated with the programme could be considered to have been inappropriate, and thus render the audit programmes in breach of Clause 18.1 of the 2003 Code. In addition, its investigations had indicated that at that time the internal instructions to the sales force did not undergo the appropriate certification process required by the Code (supplementary information, section 18.1.8). Procter & Gamble took this matter very seriously and regretted that such infringements had occurred. The necessary steps to remedy these failings were already in hand.

Recognising the need to improve the rigour of its approval process for non-standard promotional materials, the ABBH introduced a new electronic system for the approval of promotional materials in October 2005. Procter & Gamble internal sales direction communications were now included in the system and all materials used in the most recent programmes had been approved.

Clause 3.1

The complainant alleged a breach of Clause 3.1, since 'a substantial portion of the ABBH nurse programme was concerned with steroid-induced osteoporosis'. Procter & Gamble noted that Actonel was available as 5mg, 30mg, and 35mg tablets. The 5mg tablets were indicated for corticosteroid-induced osteoporosis as well as PMO. The 35mg tablet was approved in January 2003 and was indicated for PMO. The 30mg tablet was indicated for treatment of Paget's disease of bone.

There was no suggestion or evidence that the audit programmes were used to promote the use of Actonel or any other therapy as part of the programme. It was true that one of the criteria used to identify osteoporotic patients was the use of corticosteroids, in line with the RCP guidelines. However, the representative played no part in the identification of patients, or decisions on their treatment, and the audit programmes were never used to promote the use of any specific medicine. On identification by the nurse of a patient with corticosteroid-induced osteoporosis, the treatment options for that patient were determined by her GP. This might have been Actonel 5mg tablets, in accordance with the licensed indications.

Clause 2

These respectable support programmes, provided as a service to medicine, were designed and implemented to address an NHS need for the benefit of patients. It appeared, from the certified documents, that under the 2001 and 2003 Codes the services had not brought discredit upon the industry.

Summary

In conclusion, this valuable service to medicine did not directly link service provision to product usage. The service was implemented by independently trained and appropriately qualified nurses. The osteoporosis review did not compromise clinician choice or patient safety, as all clinical management decisions were left to the doctor and patient. As a disease management audit, all treatment options were available to the doctor.

Applying the requirements of the 2001 and 2003 Codes, it appeared from the documents available that the services did not act as an inducement for the doctor to prescribe Actonel since neither the materials provided to surgeries nor the discussions held with the GPs linked the promotion of Actonel or the doctor's prescribing habits with the service provision.

It was acknowledged that some of the historical internal materials might not have complied with the Code. Also the review and certification of internal documents was incomplete. In view of this, Procter & Gamble's internal procedures were undergoing comprehensive review, and new training would be provided to ensure that such situations could not arise in the future.

In response to a request for further information with regard to the Nurse Audits document supplied by the complainant (ref CP&S UK MDO), Procter & Gamble submitted it was created within the company on 7 May 2004. The reference code strongly suggested that this was a Procter & Gamble document, as this was clearly company terminology describing the UK head office based commercial team - Customer Planning and Strategy.

The document was stored in an archive of draft and final documents used at 2004 sales conferences. The archived documents relevant to the nurse audit programme included a presentation by the project leader, draft and final documents for the March 2004 sales conference and a proposed agenda for the May 2004 sales conference including details of a portion of the meeting to be led by the Procter & Gamble and Aventis commercial managers responsible for the nurse audit programmes.

Procter & Gamble did not believe that the document provided by the complainant was shared with representatives, since it was created in May 2004 and was not mentioned in the agenda for the May meeting. It was highly likely that it was only used as a positioning document for the head office team.

With regard to the certification arrangements for materials used externally in the audit programmes, the agreed, appropriate procedure was that Aventis and Procter & Gamble certified such materials. A template signatory sheet which was used in 2004 was provided. The originator company (ie Procter & Gamble or Aventis) filed the original document and a copy was sent to the partner for duplicate filing.

Core product training manuals were approved using standard copy approval procedures and final certification (by both ABBH partners) prior to dissemination. However, sales direction regarding programmes such as the nurse audit, were not consistently reviewed and/or certified at that time. This oversight had since been rectified. Due to the time elapsed, and changes in company personnel, it was not possible to declare that all sales directions and related materials issued by either company were known to the other party.

Procter & Gamble acknowledged that not all internal briefing materials were certified appropriately. Specifically, this admission applied to Clause 14.1, as referenced in point 8 of the supplementary information to Clause 18.1. The company did not admit to a breach of Clause 18.1. In addition, as previously stated, all materials provided to the medical community complied with the Code. For this reason, Procter & Gamble did not believe that the programme brought discredit upon, or reduced confidence in the pharmaceutical industry and hence did not in its view represent a breach of Clause 2.

PANEL RULING

The Panel considered that the complaint concerned both the nurse audit and the associated TOPCAT service.

The Panel noted that the nurse audit, which ran from 2002 until 2004, was sponsored by the ABBH which comprised Procter & Gamble and Aventis. Aventis had since merged with Sanofi to become Sanofi-Aventis.

The Panel noted that the material for health professionals referred to the ABBH and bore a declaration of sponsorship which referred to Aventis and Procter & Gamble. Some of the documents provided by the complainant referred to the ABBH.

The Panel noted that the nurse audit ran from 2002 until 2004. Clauses 2, 3.1 and 18.1 of the 2003 Code were the same as Clauses 2, 3.1 and 18.1 of the 2001 Code. Thus the Panel considered the matter under the 2003 Code. The supplementary information to Clause 18.1 of the 2001 Code was the same as the supplementary information to Clause 18.1 of the 2003 Code ie that medical and educational goods and services which enhanced patient care or benefited the NHS could be provided within certain conditions. The 2006 Code was changed to make it clear that medical and educational goods and services which benefited the NHS had, at the same time, to maintain patient care.

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 results 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 Panel noted that the cases now before it were being considered under the 2003 Code using the 2006 Constitution and Procedure.

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The Panel noted Procter & Gamble's submission regarding the roles of each party ie the ABBH developed the materials for the programmes and paid for the nurses. Materials used externally were copy approved by the ABBH. Procter & Gamble also stated that sales representatives from the two companies identified surgeries for inclusion in the programmes. In this regard Procter & Gamble referred to the Actonel GP Call Agenda and Follow Up document and the Programme: Update and Changes to Osteoporosis Review document. TOPCAT was agreed and sponsored by the ABBH. The ABBH representatives could nominate practices for TOPCAT which was executed by Procter & Gamble.

The Panel noted that Procter & Gamble acknowledged that as far as it was aware the Nurse Audits document (ref CP&S UK MDO) supplied by the complainant had been created within Procter & Gamble on 7 May 2004. The document clearly linked the provision of the service to the prescription of Actonel. The objectives included increasing sales by identifying new patients in Actonel friendly surgeries and to increase Actonel new patient share post audit. A section of the document was entitled 'Business Return'; the final two points made in that section were '80% of new o/p patients get Actonel – national figure 25%' and 'Increase in 35mg Actonel share from 6.6% to 26.9%'. Surgeries were nominated for the service if they were 'Actonel friendly'.

The TOPCAT Surgery Nomination Form (provided by the complainant), in a section entitled 'Checklist' also referred to Actonel - one of the checklist statements was 'Surgery preferred bisphosphonate therapy for all licensed indications is Actonel'. Completed forms were to be sent to 'your regional manger copying in ABBH colleagues'. The Panel noted Procter & Gamble's submission that the reference number on this document (ACT 7330504) suggested that it had gone through the copy approval process. A flow chart for selection of TOPCAT surgeries bore an identical reference number (ACT7330504) and instructed representatives to check first of all 'Is this Surgery First Line?' The TOPCAT Briefing Document, for internal use only, (provided by the complainant) had a reference number (ACT 8070904) and appeared to be aimed at representatives. Procter & Gamble had not commented on this document which stated that the service was for use 'where Actonel is first line'. TOPCAT was designed to complement the nurse audit programme which was described as a major strategic investment for the ABBH. It stated that based on a surgery with 5,000 patients TOPCAT would deliver an average 25 patients suitable for Actonel initiation which translated into an extra £5,200 on yearly sales per practice. It referred to the ABBH, set out a suggested sales story and stated 'representatives of Aventis (and P&G) will not …' be present or involved in certain activities.

The Panel noted Procter & Gamble's submission that it could find no evidence that the Nurse Audits document, nor the TOPCAT Surgery Nomination Form, had been supplied to the sales force'. The Panel further noted Procter & Gamble's submission that it was highly likely that the Nurse Audits document was only used as a positioning document for head office staff, however the document addressed the representatives directly, referring to 'your RBM' and summarized the representatives' role beneath the heading 'process'. The Panel queried whether such references were consistent with a head office positioning document.

The company had not commented on the TOPCAT Briefing Document. The Panel noted Procter &

Gamble's submission that internal documents encouraged representatives to identify 'Actonel first use surgeries' or 'Actonel friendly surgeries' for the nurse audit programme or TOPCAT and also that representatives should be confident that GPs would be likely to prescribe risedronate before nominating practices for inclusion in the programme. In that regard the company provided a document, Actonel GP Call Agenda and Follow Up – November 02 to January 03, which clearly showed that only when surgeries agreed to prescribe Actonel first choice or first line, were they offered the nurse audit service. The Programme: Update and Changes to Osteoporosis Review (ref A2121), was printed on Aventis and Procter & Gamble headed paper and signed by the Actonel team. It stated that assessment of the surgeries already reviewed showed there to be an increased proportion of patients already receiving bisphosphonate treatment compared to the pilot. This reduced the number of patients in each surgery that could benefit from the review. Therefore the quality of nominations needed to improve. The accompanying Sales Force Call Agenda (June 2003) (also with the reference code A2121) again clearly linked the offer of the service to those practices which agreed to prescribe Actonel first choice.

The Panel noted that having selected practices on the basis that they prescribed Actonel first choice/first line, the documents given to customers in respect of the nurse audit programme and TOPCAT did not refer to Actonel. These documents referred to a selection of treatments; bisphosphonate, selective oestrogen-receptor modulator (SERM) and calcium and Vitamin D supplement of choice.

The Panel considered that the internal documents for the nurse audit and for TOPCAT did not meet the requirements of Clause 18.1 of the 2003 Code. The documents were such that representatives would only offer the services to those surgeries that agreed to use Actonel first choice/first line. In that regard the Panel noted that Procter & Gamble had data to show that 88% of all treated patients were initiated on Actonel in the nurse audit programme between March 2003 and October 2004. In 2004 approximately 60 patients were started on Actonel as a result of TOPCAT. The Panel considered that the selection of practices for the nurse audit and TOPCAT was unacceptable and this meant that the arrangements were contrary to the requirements of Clause 18.1 and ruled accordingly. This ruling was appealed.

The Panel further considered that the overall arrangements brought discredit upon the pharmaceutical industry; a breach of Clause 2 was ruled. This ruling was appealed.

The Panel decided to report Procter & Gamble to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the 2006 Constitution and Procedure. With regard to the promotion of Actonel for corticosteroid-induced osteoporosis, the Panel noted that throughout the period of the nurse audit and of TOPCAT, Actonel 5mg was so licensed. Although Actonel 35mg was not licensed for use in corticosteroid-induced osteoporosis, there was no evidence that it had been promoted for such an indication. No breach of Clause 3.1 was ruled.

Case AUTH/1902/10/06 - Sanofi-Aventis

The service offerings in question had been run by Aventis prior to its merger with Sanofi. The Panel noted Sanofi-Aventis' submission that none of its current management team had been involved with the nurse audit; no-one from Aventis' medical or regulatory teams had transferred to the new company which had no involvement in the pre-2005 ABBH when the documents at issue were created and used. The Panel considered that Sanofi-Aventis was, nonetheless, responsible for the acts or omissions of Aventis in the past which came within the scope of the Code. Sanofi-Aventis had had to rely on incomplete records archived by Aventis to form its response. Procter & Gamble had provided Sanofi-Aventis with a copy of its response.

The Panel noted Sanofi-Aventis' comments about the logistical and other difficulties associated with the merger. Nonetheless, given Sanofi-Aventis' continuing responsibilities under the Code for acts/omissions of Aventis it was beholden upon companies wherever possible to use their best endeavours to ensure that relevant material and job bags were retained. Sanofi-Aventis should at the very least have been able to produce job bags for the relevant training material from early 2004.

The Panel noted Sanofi-Aventis' submission that it had no archived record of the documents supplied by the complainant ie the Nurse Audits document, the TOPCAT Surgery Nomination Form and the TOPCAT Briefing Document. (The first document was acknowledged by Procter & Gamble, as far as it was aware, to have been drafted by it. Procter & Gamble acknowledged that the second document appeared to have gone through its certification process. In the Panel's view the TOPCAT briefing document was likely to have gone through Procter & Gamble's certification process given the similarity of its reference code to the reference code on the other two documents.) In its response Sanofi-Aventis submitted documents supplied to customers.

Nonetheless the Panel noted that the Nurse Audits document, the TOPCAT flow chart, the TOPCAT Surgery Nomination Form and TOPCAT Briefing Document were originally provided by the complainant who described himself as a current employee of Sanofi-Aventis. He corresponded with the Authority under a pseudonym. The Panel was thus extremely cautious when deciding what weight to attribute to this evidence. The provision of relevant documents by a current Sanofi-Aventis employee might be seen as inconsistent with the company's comments on the availability of documents. Nonetheless the Panel did not know how or from where the complainant had obtained the documents.

The Panel further noted Sanofi-Aventis' submission that the ABBH was a collaboration between two independent companies and that as such it was likely

that the two had differing involvement and participation in particular initiatives relating to Actonel. The Panel noted, however, that Procter & Gamble had submitted the Programme: Update and Changes to Osteoporosis Review document (ref A2121), which clearly linked the two companies (it was written on notepaper headed with the two company logos) and which in the accompanying Sales Force Call Agenda (June 2003) clearly linked the provision of the nurse audit service to the prescription of Actonel ie call objective was to gain agreement to prescribe Actonel as first choice. The Sales Force Call Agenda referred to completing the booking form with input from 'local Alliance territory team including opposite Alliance RBM/RSM, P&G Account Executive and Aventis Hospital Rheumatology Team'. Weekly update reports would be sent to 'all Alliance RBM/RSMs including approved nominations tracker…'.

The Panel considered that the Programme: Update and Changes to Osteoporosis Review document did not meet the requirements of the Code. Sanofi-Aventis had been provided with a copy of Procter & Gamble's response by Procter and Gamble. The Authority had asked Sanofi-Aventis to comment on any differences. Sanofi-Aventis had not commented on this specific document. The document encouraged representatives to only offer the service to those surgeries which used Actonel as first choice. The Panel noted its comments above on the TOPCAT documents which referred to the ABBH and to Aventis. The Panel considered that the selection of practices for the nurse audit and TOPCAT were unacceptable and this meant that the arrangements were contrary to the requirements of Clause 18.1 and ruled accordingly. This ruling was appealed.

The Panel further considered that the overall arrangements brought discredit upon the pharmaceutical industry; a breach of Clause 2 was ruled. This ruling was appealed.

The Panel decided to report Sanofi-Aventis to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the 2006 Constitution and Procedure.

With regard to the promotion of Actonel for corticosteroid-induced osteoporosis, the Panel noted that throughout the period of the nurse audit and of TOPCAT, Actonel 5mg was so licensed. Although Actonel 35mg was not licensed for use in corticosteroid-induced osteoporosis, there was no evidence that it had been promoted for such an indication. No breach of Clause 3.1 was ruled.

Case AUTH/1902/10/06

APPEAL BY SANOFI-AVENTIS

Sanofi-Aventis appealed the Panel's rulings of breaches of Clauses 18.1 and 2 of the 2003 Code.

Sanofi-Aventis explained that the programmes offered medical services which were in demand, to assist practices in better identifying patients at risk of osteoporosis and then confirming diagnosis, at a time when the NHS would not have funded such services at all. An independent agency which employed and trained nurses managed both the services and contacts with prescribers, independently of representatives and the ABBH, in accordance with best practice. Practitioners who requested the services were free to prescribe whichever non-medicinal or medicinal treatment they deemed most appropriate for their patient. The arrangements for the programmes did not limit access to doctors who would only prescribe Actonel as their first choice of treatment and did not breach Clause 18.1. The programmes were conducted and completed before the current management of Sanofi-Aventis took over Aventis. The programmes did not and would not bring the industry into disrepute.

Sanofi-Aventis noted that the Panel had ruled a breach of Clause 18.1, as a result of its finding that practices were selected for the nurse audit and TOPCAT programmes on the basis that representatives would only offer the services to those surgeries that agreed to use Actonel first choice/first line. Sanofi-Aventis submitted that the conclusions of the Panel were incorrect because:

- The Panel had relied upon documents that were never used by representatives or to brief representatives during the implementation of the nurse audit or TOPCAT programmes.
- Documentation in relation to the nurse audit programme had been misinterpreted.
- The programmes were not limited to practices who prescribed Actonel as their preferred choice of treatment.
- The data for individual practices did not support a contention that the nurse audit and TOPCAT programmes acted as inducements to prescribe Actonel.
- The nurse audit and TOPCAT programmes must be considered in the context of the 2003 Code.

Sanofi-Aventis submitted that further submissions in relation to these grounds would be provided in advance of the appeal hearing following consideration of preliminary procedural questions by the Chairman.

Sanofi-Aventis submitted that the Panel had provided no reasoning to justify its finding of a breach of Clause 2, simply stating that 'the overall arrangements brought discredit upon the pharmaceutical industry'. The supplementary information to Clause 2 stated 'a ruling of a breach of this clause is a sign of particular censure and is reserved for such circumstances'. In this context, fairness required that the Panel should provide reasons explaining its conclusion that the circumstances of this case warranted such censure. Sanofi-Aventis disagreed with the finding of the Panel. Moreover, it was significant that, in reaching its conclusion with respect to Clause 2, the Panel had not mentioned the following three issues which should properly have been considered:

Firstly the very substantial benefits both to patients and to the NHS resulting from the programmes and the fact that participating doctors were clearly free to

prescribe whatever medicine they chose or to prescribe no treatment. Sanofi-Aventis noted a GP's statement that 'this kind of service represents true partnership between the NHS and pharmaceutical industry'. Secondly, the fact that, following the conclusion of the nurse audit and TOPCAT programmes, Sanofi-Aventis and its current directors had no involvement with the matters which were the subject of complaint. And thirdly it was also relevant that the procedures followed by Aventis were modified following the merger. These matters, which were directly relevant to the culpability of the merged company and its current directors, had not seemingly been taken into account by the Panel in considering its ruling in relation to Clause 2.

Sanofi-Aventis took a finding of a breach of Clause 2 extremely seriously and submitted that it should be reserved for cases where it had proper meaning. In circumstances where neither Sanofi-Aventis nor any of the current directors of the company had any involvement in or opportunity to influence the programmes that were the subject of complaint, a finding of a breach of Clause 2 was inappropriate.

Sanofi-Aventis submitted that the ruling of the Panel in relation to Sanofi-Aventis, with respect to the nurse audit and TOPCAT programmes, was incorrect and it requested that the Panel's rulings in respect of breaches of Clauses 18.1 and 2 of the 2003 Code, were set aside by the Appeal Board.

FURTHER SUBMISSION BY SANOFI-AVENTIS

Sanofi-Aventis noted that the programmes at issue were run as services to medicine, by the ABBH which was set up in 1997 in the US and subsequently in the UK by Procter & Gamble and Hoechst Marion Roussel, to share know-how and certain costs (including sales force, promotional and non-promotional services) relating to the marketing of Actonel for the treatment of osteoporosis. In 1999, Hoechst Marion Roussel merged with Rhone Poulenc Rorer to form Aventis. Since that time, the two participants in ABBH in the UK had been Procter & Gamble and Aventis Pharma Limited. During that time Sanofi was the UK subsidiary of Sanofi, an independent pharmaceutical company. It was only in the first quarter of 2005 that Sanofi's operations were merged with those of Aventis.

Sanofi-Aventis noted that in October 2006, the Authority wrote to Sanofi-Aventis, regarding an anonymous complaint received in relation to a nurse audit programme, run by ABBH between 2002 and 2004. The letter from the Authority stated a current employee at Sanofi-Aventis had complained under the Code regarding the ABBH nurse audit programme using a pseudonym. An anonymised copy of the letter of complaint was enclosed with the letter from the Authority, together with various documents provided by the anonymous complainant. (These documents in fact related to two separate audit programmes, the nurse audit programme and TOPCAT which were described below).

The complainant subsequently sent a second letter to the Authority making further allegations in respect of activities by ABBH. The Panel had ruled no breach of the Code regarding these latter allegations.

Investigation of the complaint by Sanofi-Aventis

Sanofi-Aventis submitted that both it and Procter & Gamble experienced substantial difficulties investigating the matters raised by the anonymous complainant as the programmes had been concluded and between 2 and 5 years had elapsed following the matters which were the subject of the complaint.

Sanofi-Aventis submitted that the prejudice resulting from the delay had been heightened as, during the relevant period, the company had undergone substantial changes which affected the availability of documents and evidence from staff. The acquisition of Aventis by Sanofi took place in December 2004, shortly after the relevant programmes were concluded. At the time of the acquisition, many Aventis personnel left the company; in particular, none of the medical or regulatory teams transferred to Sanofi. No member of the current management of Sanofi had worked for Aventis prior to the acquisition or had any involvement in the programmes referenced in the complaint. Furthermore, Aventis documentation and electronic files were lost whilst under Aventis' control.

Sanofi-Aventis submitted that the information available to it in relation to issues raised by the anonymous complainant were therefore incomplete and the company's ability to investigate the allegations raised had been limited as a result of corporate reorganisation, staff departures and changes in management and other personnel.

Programmes referred to in the complaint

Sanofi-Aventis noted that the documentation provided by the anonymous complainant related to two programmes run by the ABBH, a nurse audit and TOPCAT, both of which reflected government policy to improve the diagnosis and management of patients with osteoporosis. The importance of this therapeutic area was emphasised in 1999 in the Secretary of State for Health's White Paper 'Saving Lives: Our Healthier Nation' which highlighted the significance of osteoporosis as a major cause of death and disability in older people. In the National Service Framework for Older People, issued in March 2001, Standard 6 focused on reducing the number of falls which result in serious injury. One of the key aspects of a strategy to reduce injury associated with falls was for GPs to take responsibility for assessing risk of osteoporosis and identifying those who required prevention or treatment. However, despite the importance placed upon the appropriate treatment of patients at risk of osteoporosis, at the time relevant to the complaint, doctors were under-resourced to make such diagnoses. In particular, the availability of dual X-ray absorpiometry (DXA) to measure bone mineral density and predict fracture risk, was severely limited. In the absence of DXA scanning, doctors at that time, were unable to diagnose patients at risk of osteoporosis.

In these circumstances, Sanofi-Aventis submitted that the programmes offered by Aventis and Procter & Gamble provided a valuable service to medicine and the NHS and substantial benefits to patients. In this regard Sanofi-Aventis referred to statements from doctors who reviewed and participated in the programme. Similar services were provided at the time by other companies which supplied treatments for osteoporosis in the UK.

Nurse Audit Programme

The nurse audit programme was run by an independent organisation which specialised in providing audit protocols and reports for general practices. The programme followed a detailed protocol, incorporating best practice guidelines, including Primary Care Rheumatology Guidelines and guidelines issued by the RCP. An explanation of the nurse audit programme was provided in a statement by a Procter & Gamble employee (as provided by Procter & Gamble) supported by an email from a research nurse in clinical gerontology.

Sanofi-Aventis submitted that the programme was run in two phases. During phase 1, patients with established osteoporosis and/or a high risk of fracture (including patients on long term oral steroids, patients with confirmed osteoporosis on calcium supplements alone, patients with radiographic evidence of bone loss or vertebral deformity, etc and patients with a previous fragility fracture) would be assessed by the nurses as requiring immediate treatment. In phase 2, patients with osteoporosis risk factors but with an unconfirmed diagnosis, would be invited for DXA scanning and consultation with nurses. Following the review, the nurse would provide the GP with a final report collated from the records and patient reviews. The GP would then decide which treatment, if any, should be offered to patients with osteoporosis.

Representatives employed by ABBH partners were not involved in the programme and did not have access to any materials arising from it. Representatives discussed the existence of the programme with practices in non-promotional calls. The nurse audit programme commenced as a pilot service in late 2001 and was discontinued on 31 October 2004.

TOPCAT

Sanofi-Aventis submitted that the TOPCAT programme also aimed to assist GPs to identify patients at risk of osteoporosis, but used software rather than nurses to analyse patients' records. The programme was applied by the GP or by an independent organisation. An explanation of the TOPCAT programme was provided in the statement of a Procter & Gamble employee (as provided by Procter & Gamble).

Sanofi-Aventis submitted that the third party staff or the GP would use the TOPCAT software to identify patients at risk of osteoporosis. A patient so identified would be reviewed by the GP who would agree a management strategy for that patient, which might include further investigation or clinical review, advice regarding smoking cessation, prescription of vitamin D or other osteoporosis treatments.

Sanofi-Aventis submitted that again, the involvement of ABBH representatives was limited to an initial discussion, during the course of a non-promotional visit, regarding the availability of the service. At no time did any employee of ABBH companies have access to information about patients, nor any participation in any subsequent prescribing decision by the GP.

Grounds for appeal

Sanofi-Aventis submitted that a feature of this complaint was the fact that the name of the complainant was not made known to the Authority, which was provided only with a pseudonym. Whilst the complainant claimed to be a current employee of Sanofi-Aventis, although one who did not work in the osteoporosis part of the business, it was unclear whether the Authority had been able to confirm these details, or the source of the documents provided by the complainant in relation to the nurse audit and TOPCAT programmes. Furthermore, the Panel had seemingly relied upon the unsubstantiated evidence of the anonymous complainant in the following respects:

- In concluding that documents provided by the complainant, specifically the Nurse Audits document (ref CP&S UK MDO) and the TOPCAT Briefing Document (ref ACT8070904), the flowchart for selection of TOPCAT surgeries (ref ACT7330504 A2541) and the TOPCAT Surgery Nomination Form (ref ACT7330504 A2541) were used to brief representatives in relation to the nurse audit or TOPCAT programmes. The explanations provided by Sanofi-Aventis and Procter & Gamble, as to why they considered such documents were not used to implement the programmes, had not been addressed by the Panel.

- In suggesting that the disclosure provided by Sanofi-Aventis had been incomplete, the Panel had seemingly relied upon the assertion of the complainant that he was a current employee of Sanofi-Aventis and the fact that he provided documentation, which he claimed was used in implementing the programmes, that could not be located by the company.

The explanations provided by Sanofi-Aventis were supported by evidence:

- Witnesses (including a Procter & Gamble employee who contributed to the development of the nurse audit programme; another Procter & Gamble employee who was involved in the running of the TOPCAT programme; doctors who reviewed and participated in the programmes; and a technician who carried out DXA scanning as part of the nurse audit).

- Sales IMS data confirming the prescribing patterns of the practices which participated in the programmes.

- The explanations of the companies as to how the documents relied upon by the Panel should properly be interpreted.

In the context of this evidence, Sanofi-Aventis submitted that it was simply not open to the Panel to rely upon unsubstantiated inference based on an anonymous complaint that might not be tested through cross-examination. Sanofi-Aventis provided an opinion from a Queen's Counsel (QC).

Sanofi-Aventis submitted that the Panel made various assertions which were unreasoned and unclear. Sanofi-Aventis had requested that sufficient explanations and/or reasons be provided in advance of the appeal hearing so that the company might consider the basis for the decision of the Panel and appropriately prepare its submissions for the appeal. However, the information requested had not been made available to the company.

Sanofi-Aventis noted that the Panel had ruled a breach of Clause 18.1 of the Code by both it and Procter & Gamble as a result of the findings that the selection of practices for the nurse audit and TOPCAT programmes indicated that 'representatives would only offer the services to those surgeries that agreed to use Actonel first choice/first line'.

Sanofi-Aventis submitted that the Panel had confirmed that the documents given to doctors in respect of the nurse audit and TOPCAT programmes did not refer to Actonel and were not objectionable. However, the Panel seemingly failed to recognise the very substantial benefits gained by patients and by the NHS as a result of the nurse audit and TOPCAT programmes. These benefits were clear from the statement of the Chairman of the National Osteoporosis Society Primary Care Forum who assisted in the development of the programmes. His statement confirmed, 'the audit service provided by ABBH has assisted practices to identify patients at risk of osteoporosis using [guidelines from the RCP and NICE]. The independent nurses and DXA scanning services have helped overcome the capacity issues facing the NHS'. Other doctors who participated in the programmes had also confirmed their views.

Sanofi-Aventis submitted that in reaching its conclusions with respect to Clause 18.1, the Panel relied on various documents provided by the complainant or disclosed by Procter & Gamble. None of these documents were located by Sanofi-Aventis and the current management of the company had no direct knowledge of them. Furthermore, reliance on these documents and their interpretation by the Panel was inappropriate for the following reasons:

Sanofi-Aventis submitted that the Nurse Audits document (Ref CP&S UK MDO) was seemingly generated by Procter & Gamble in May 2004. A copy of the document was found by Procter & Gamble in a file containing draft documents and final material used for a sales conference in May 2004, although it did not appear that the document was used at the conference. In the context of the reference at the bottom of the document which indicated that it was created for the UK head office based commercial team - Customer Planning and Strategy, Procter & Gamble submitted that the document was used only for internal purposes at its head office (specifically to obtain the support of management to the continuation of the programme). In May 2004, the person responsible for the nurse audit programme at Procter & Gamble no longer worked with the company. He was, at that time, subject to a performance review and his work was closely supervised. Any documents generated by him that were intended to be released to the sales force would have been first reviewed by his line manager who had confirmed that, prior to this investigation, she had not seen the nurse audit document. This evidence strongly suggested that the document was used only for internal purposes. Moreover there was no positive evidence that this document was used to brief representatives.

Sanofi-Aventis submitted that while the anonymous complainant had produced various documents in relation to the TOPCAT programme (a TOPCAT Briefing Document, a Flowchart for Selection of TOPCAT Surgeries and a TOPCAT Surgery Nomination Form) from an unidentified source, there was no evidence that any of this material was ever used to brief representatives or otherwise in implementing the programme.

Sanofi-Aventis submitted that the Programme: Update and Changes to Osteoporosis Review document, was located by Procter & Gamble amongst its documents. In its decision, the Panel referred to the sentence in that document which stated that 'assessment of the surgeries already reviewed showed there to be an increased proportion of patients already receiving bisphosphonate treatment compared to the pilot. This reduced the number of patients in each surgery that could benefit from the review. Therefore the quality of nominations needed to improve'. The Panel did not explain the apparently adverse inference it had drawn from this wording and Sanofi-Aventis was therefore prejudiced in its ability to respond. However, while Sanofi-Aventis had no direct knowledge of this document, in circumstances where the aim of the nurse audit programme was to identify and investigate women at risk of osteoporosis, where the diagnosis was unrecognised, it was self-evident that an increase in the proportion of patients taking bisphosphonates would indicate a higher proportion of patients already reviewed by the GP and a smaller number who would therefore benefit from the audit. In the context of a limited budget it was clearly appropriate for the programme to be directed towards practices where the greatest number of patients might benefit and, in these circumstances, no adverse inferences should be drawn from the wording of the document. Sanofi-Aventis referred to the background information provided by a Procter & Gamble employee which stated:

'While I was not involved in the preparation of the [Programme: Update and Change to Osteoporosis Review] dated June 2003, a further document provided to the PMCPA by Procter & Gamble Pharmaceuticals, I am aware of the history behind its content. Following the pilot

Programme we assessed the efficiency of the arrangements. At this stage it became clear that the costs incurred in providing the audit service were much higher per patient with surgeries which had small list sizes. This was because there were fixed costs associated with audit which were the same whatever the size of the practice; e.g. introductory meeting (1 day), final presentation of the results to the practice (1 day) and the use of the DXA scanner (where costs were the same whether 4 patients or 14 patients were scanned in a day). Additionally small surgeries tended not to have a practice manager and were not fully Read Coded; therefore note searching in these practices was slow and inefficient. Accordingly, we made a decision to concentrate the programme on practices with larger patient lists where more patients could benefit within our budget.'

Sanofi-Aventis noted that the Panel subsequently referred to the Sales Force Call Agenda (June 2003) also located by Procter & Gamble and disclosed to the Authority. The Panel asserted that this document 'clearly linked the offer of the service to those practices who agreed to prescribe Actonel first choice'. This interpretation of the document was incorrect. The agenda envisaged that a sales call would be undertaken where the objective was to 'gain agreement to prescribe Actonel as first choice therapy…'. However, there was no link in the document between that sales call and the subsequent assessment of suitability for osteoporosis review. The list of factors to be considered in relation to the assessment of suitability for participation in the nurse audit, as set out in the agenda, did not include any requirement that the practice had in fact agreed to prescribe Actonel as first choice therapy or at all. Furthermore, it was significant that the Osteoporosis Surgery Booking Form also provided to the Authority included no requirement that the practice had agreed to prescribe Actonel first line. Sanofi-Aventis submitted that in these circumstances the inferences drawn from the documents by the Panel were unfair.

Sanofi-Aventis submitted that the Panel had been wrong to conclude that the nurse audit and TOPCAT programmes were offered only to those surgeries that agreed to use Actonel first line. In fact, practices which did not prescribe Actonel first line were also nominated and did participate in the programmes. In its defence, Sanofi-Aventis provided the Authority with a statement from a doctor who confirmed that this was the case and this had been reiterated by that doctor and by other doctors who participated in the programme.

Furthermore, Sanofi-Aventis had seen data obtained by Procter & Gamble in relation to the prescription of bisphosphonates by practices who participated in the nurse audit programme. This data provided definitive proof that ABBH did not limit participation to practices where Actonel was prescribed first line. The data confirmed that in a significant proportion of the practices, Actonel prescriptions comprised only a tiny percentage of the number of bisphosphonate prescriptions issued and in a number of practices which participated, Actonel was not prescribed at all.

Sanofi-Aventis provided two graphs showing the share of the bisphosphonate market attributable to Actonel in each of the practices which participated in the nurse audit programme. Between January and June 2002, the graph indicated that none of the practices which participated used Actonel first line. The graph covering the period between July and December 2004 indicated that whilst Actonel's market share had increased from 2002, it still remained the position that approximately one third of practices which participated in the nurse audit programme, prescribed Actonel at a rate lower than the national average.

Sanofi-Aventis submitted that in view of the fact that doctors could be supplied with TOPCAT to implement themselves, it was not possible to obtain and interpret sales data over a period in a similar way for TOPCAT. However, sales data obtained by Procter & Gamble confirmed that TOPCAT was not offered only to practices that prescribed Actonel first line and that the share of bisphosphonate market attributable to Actonel in participating practices was broadly in line with the national market share.

Sanofi-Aventis submitted that these data clearly demonstrated that neither the nurse audit programme nor the TOPCAT programme imposed a requirement that Actonel should be prescribed first line before practices could be nominated for inclusion.

Sanofi-Aventis noted that the Panel had relied upon data obtained by Procter & Gamble, which showed that 88% of treated patients were initiated on Actonel in the nurse audit programme between March 2003 and October 2004 (and that approximately 60 patients were started on Actonel as a result of TOPCAT in 2004), in reaching its conclusion that the programmes did not meet the requirements of Clause 18.1 of the 2003 Code.

Sanofi-Aventis submitted that the 88% figure referred to in Procter & Gamble's response was not credible. The data which formed the basis for this figure had not been shown to Sanofi-Aventis and was not now available to Procter & Gamble; it was wholly inconsistent with sales data. In these circumstances and in the context of the sales data, the figure of 88% was more likely to refer to the number of patients prescribed a bisphosphonate, following the nurse audit rather than the number prescribed Actonel.

Sanofi-Aventis submitted that in addition, during the TOPCAT programme, 2,956 patients were identified as being at risk of osteoporosis in 2004 and of these only approximately 60 patients (some 2.3%) were prescribed Actonel. While it was unclear what percentage of patients were prescribed any treatment, on no view did a prescribing rate of 2.3% of patients identified to be at risk of osteoporosis suggest that the TOPCAT surgeries were selected on the basis that Actonel would be prescribed first line or that participation in the programme constituted an inducement to prescribe contrary to Clause 18.1. Indeed, the data suggested the opposite.

Sanofi-Aventis submitted that statements from individual doctors involved with the programme

confirmed that the offer was not linked to prescribing of Actonel. Moreover, while one of the doctors was unable, as a result of the passage of time, to remember details of the programme, data confirmed that the rates of prescribing at his surgery remained broadly the same throughout the period when the nurse audit was conducted. Jan - June 2002: 16%; July - Dec 2002: 9%; Jan - June 2003: 15%; July - Dec 2003: 22%; and July - Dec 2004: 17%. In these circumstances, it was clear, contrary to the conclusions of the Panel, that the nurse audit and TOPCAT programmes did not act as an inducement to prescribe Actonel.

Sanofi-Aventis submitted that while the evidence demonstrated clearly that practices were not selected for inclusion in the nurse audit and TOPCAT programmes only if they were willing to prescribe Actonel, even if the Appeal Board was to make a contrary finding it did not of itself constitute a breach of Clause 18.1 of the 2003 Code.

Sanofi-Aventis noted that supplementary information to Clause 18.1 of the 2003 Code stated that this 'does not prevent the provision of medical and educational goods and services which will enhance patient care or benefit the National Health Service'. Such services were welcomed by the Government and by the NHS and the Panel did not suggest they were objectionable. It was absolutely clear that the nurse audit and TOPCAT programmes provided a valuable service to the NHS in circumstances where the resources to identify patients at risk of osteoporosis, through DXA scanning, were limited and that patients derived substantial benefit from these programmes. However, it was self-evident that services to medicine would not be provided by companies if the result was to benefit their competitors at their own expense. The result of the Panel's approach was that such programmes would be offered only by companies whose products had a majority market share, where the programme would not advantage their competitors. This was clearly undesirable.

Sanofi-Aventis noted the supplementary information to Clause 18.1 of the 2003 Code stated 'the provision of such goods or services must not be done in such a way as to be an inducement to prescribe, supply, administer, recommend or buy any medicine…'. Extensive guidance was provided to assist companies in relation to medical and educational goods and services. It was noteworthy that at no place did the Code or its supplementary information suggest that the provision of medical goods and services might not be made available to practices that already prescribed a company's products, in circumstances where the doctor was free to prescribe any medication or no medication, as he saw fit. The revisions to the Code introduced in 2006 included no such wording.

Sanofi-Aventis submitted that if, in the circumstances described above, the Authority believed that services to medicine offered by a company to practices which prescribed or who were willing to consider prescribing that company's products, constituted a breach of Clause 18.1 of the Code, this view should be clearly stated in the supplementary information. In the absence of any guidance indicating that such arrangements were objectionable, it was unfair for the Panel to give a ruling adverse to Procter & Gamble and Sanofi-Aventis in circumstances where the programmes themselves were valuable and created no obligation for a participating doctor to prescribe Actonel or any medicine.

In summary, Sanofi-Aventis submitted that, the overwhelming weight of the evidence indicated that the nurse audit and TOPCAT programmes were provided as services to medicine, to fulfil clinical need and to benefit patients in the NHS. Practices which did not prescribe Actonel first line were not excluded from the programmes and there was absolutely no evidence that these programmes in any way constituted an inducement to prescribe, contrary to Clause 18.1.

Sanofi-Aventis submitted that a finding of a breach of Clause 18.1 did not necessarily result in a ruling that Clause 2 had been breached. However, in this case, the Panel had provided no reasoning to justify the finding of a breach of Clause 2 in respect of both companies, simply stating that 'the overall arrangements brought discredit upon the pharmaceutical industry'. Sanofi-Aventis emphatically disagreed that this was the case. The supplementary information to Clause 2 stated 'a ruling of a breach of this clause is a sign of particular censure and is reserved for such circumstances'. In these circumstances, it was incumbent upon the Panel to provide proper reasons explaining the circumstances of this case that warranted such censure.

Sanofi-Aventis submitted that it was significant that, in reaching its conclusion with respect to Clause 2, the Panel had seemingly failed to take into account the following issues which should properly have been considered:

- The very substantial benefits both to patients and to the NHS resulting from the programmes and the fact that participating doctors were clearly free to prescribe whatever medicine they chose or to prescribe no treatment. In direct contrast to the findings of the Panel, a GP stated 'this kind of service represents true partnership between the NHS and pharmaceutical industry'.

- The fact that the Panel confirmed that the documents given to doctors with respect to the nurse audit and TOPCAT programmes were not objectionable.

- The fact that physicians did not perceive the programmes as inducements to prescribe, statements provided by doctors who participated in the programmes had confirmed that they did not consider the arrangements an inducement to prescribe and that they would not have participated in the programmes had they found any such inducement to be present.

- The fact that, following the conclusion of the nurse audit and TOPCAT programmes, Aventis was acquired by Sanofi, and that Sanofi-Aventis and its current management had no involvement with the matters which were the subject of complaint.

Sanofi-Aventis took a finding of a breach of Clause 2 of the Code extremely seriously, it should be reserved for cases where it had proper meaning. In circumstances where neither Sanofi-Aventis nor any member of the current management of the company had any involvement in or opportunity to influence the programmes that were the subject of complaint, a finding of breach of Clause 2 was inappropriate.

- It was also relevant that the procedures followed by the company underwent substantial revision following the merger and were wholly different from those that were in place at Aventis at the time of the nurse audit and TOPCAT programmes. These matters which were directly relevant to the culpability of the merged company and its current management had not seemingly been taken into account by the Panel in considering its ruling in relation to Clause 2.

Overall, therefore, Sanofi-Aventis submitted that the ruling of the Panel in relation to both it and Procter & Gamble, with respect to the nurse audit and TOPCAT programmes, was unreliable and unfair and it respectfully requested that the Panel's rulings in respect of breaches of Clauses 18.1 and 2 of the 2003 Code be set aside by the Appeal Board.

Case AUTH/1903/10/06

APPEAL BY PROCTER & GAMBLE

Procter & Gamble appealed the Panel's rulings of breaches of Clauses 18.1 and 2 of the 2003 Code.

Procter & Gamble submitted that its reasons for appealing included the following:

- The programmes offered medical services which were in demand, to assist practices in better identifying patients at risk of osteoporosis and then confirming diagnosis, at a time when the NHS would not have funded such services at all.
- An independent agency which employed and trained nurses managed both the services and contacts with prescribers, independently of representatives and the ABBH, in accordance with best practice.
- Practitioners who requested the services were free to prescribe whichever non-medicinal or medicinal treatment they deemed most appropriate for their patients.
- The arrangements for the programmes did not limit access to doctors who would only prescribe Actonel as first choice of treatment and did not breach Clause 18.1.
- The programmes did not and would not bring the industry into disrepute.

With regard to the Panel's ruling of a breach of Clause 18.1, Procter & Gamble submitted that the conclusions of the Panel were incorrect for the following reasons:

The Panel had relied upon documents that were never used by representatives to implement the nurse audit or TOPCAT programmes.

Investigations by Procter & Gamble had indicated that documents disclosed by the complainant and relied upon by the Panel, were only used by head office staff and were not distributed to representatives, who were instead briefed orally in relation to the nomination of practices. The briefing of representatives was conducted in accordance with the flowchart in the document 'Actonel GP Call Agenda and Follow Up November 02 to January 03' which confirmed that any discussion with doctors regarding the nurse audit programme was conducted at a separate visit from any promotion of Actonel.

Furthermore, Procter & Gamble submitted that the inferences drawn by the Panel were inconsistent with the Sales Force Call Agenda which listed the criteria to be taken into account when considering a practice for nomination to the programme; these did not include any requirement that Actonel should be prescribed the first line or at all.

Procter & Gamble had confirmed with representatives and doctors who participated in the nurse audit that (a) representatives did not only nominate practices which prescribed Actonel first line (b) participating doctors felt themselves to be free to prescribe whatever treatment was most appropriate for their patients.

Procter & Gamble submitted that the nurse audit documents had been misinterpreted. The Panel had wrongly assumed that documents for internal commercial purposes were used to brief representatives.

Moreover, certain documents (including the Sales Force Call Agenda) had been misconstrued as indicating that a pre-programme sales visit by representatives was part of the audit programme. As indicated by proper consideration of the document and confirmed by participating doctors, this was not the case; promotional activity by representatives was conducted separately from any discussion regarding the nurse audit.

Procter & Gamble submitted that the programmes were not limited to practices which prescribed Actonel first line. It was clear from the data that participating practices were not limited to those which prescribed Actonel first line.

Procter & Gamble had been able to conduct a comprehensive analysis of the data from 323 of the 351 practices that were involved in the nurse audit programme. In the average practice that participated, Actonel had an initial market share of just 14%. The market share of Actonel across the practices at the beginning of 2002 varied from 0% to 46%. Over one third (38%) of practices that took up the opportunity to be involved in the programme, prescribed Actonel at a rate below its average national share of the bisphosphonate market. These data clearly disproved the allegation that only first line and Actonel friendly practices were offered the nurse audit programme.

Procter & Gamble submitted that the position with respect to TOPCAT was similar. Data previously provided to the Authority showed that, of the patients identified as being at risk of osteoporosis in 2004, only around 2% were prescribed Actonel. Such prescribing rates were well below the national average for the product and again demonstrated conclusively that practices were not selected on the basis that Actonel was the first line bisphosphonate.

Procter & Gamble submitted that the data for individual practices did not support a contention that the nurse audit and TOPCAT programmes acted as an inducement to prescribe Actonel. The data obtained in relation to prescribing by individual practices also demonstrated that the nurse audit programme made little difference in the relative proportion of bisphosphonate prescriptions issued for Actonel. In particular, the proportion of practices which prescribed Actonel at a rate below the national average remained relatively unchanged before and after the programme.

Procter & Gamble submitted that the nurse audit and TOPCAT programmes must be considered in the context of the 2003 Code and industry practice at that time. For the reasons explained above, Procter & Gamble maintained that there was no link between the availability of the nurse audit and TOPCAT programmes and the prescription of Actonel. However, if the Appeal Board believed that it was inappropriate for a company to offer a service to medicine to a practice which might issue some prescriptions in respect of its products, then that fact should be clearly stated in the Code. It was significant that there was no exclusion of such activity in the wording of the 2003 Code and that, when the Code was revised in 2006, no additional guidance was provided in this context.

Further submissions in relation to these grounds would be provided in advance of the appeal hearing.

Procter & Gamble noted that the Panel had provided no reasoning to justify the finding of a breach of Clause 2 in respect of Procter & Gamble, simply stating that 'the overall arrangements brought discredit upon the pharmaceutical industry'. Procter & Gamble disagreed that this was the case. The supplementary information to Clause 2 stated 'a ruling of a breach of this clause is a sign of particular censure and is reserved for such circumstances'. In these circumstances, fairness required that the Panel should provide reasons explaining its conclusion that the circumstances of this case warranted such censure.

Procter & Gamble submitted that it was significant that, in reaching its conclusion with respect to Clause 2, the Panel had not mentioned four issues which should properly have been considered:

Firstly, the very substantial benefits both to patients and to the NHS resulting from the programmes. Secondly, participating doctors were clearly free to prescribe whatever medicine they chose or to prescribe no treatment and felt under no pressure to prescribe Actonel. Thirdly, physicians did not perceive the programmes as inducements to prescribe. And fourthly, Clause 18.1 of the 2003 Code had not specifically excluded the offer of a service to medicine to those practices who already prescribed a company's products. (The 2006 version of the Code made no revision to incorporate such a requirement).

Overall, therefore, Procter & Gamble submitted that the ruling of the Panel in relation to Procter & Gamble was incorrect and it respectfully requested that the Panel's rulings of breaches of Clauses 18.1 and 2 of the 2003 Code were set aside by the Appeal Board.

FURTHER SUBMISSION BY PROCTER & GAMBLE

Procter & Gamble submitted that the programmes that were the subject of complaint were run as services to medicine by ABBH which was set up in 1997 in the US and subsequently in the UK by Procter & Gamble and Hoechst Marion Roussel, to share know-how and certain costs including sales force, promotional and non-promotional services relating to the marketing of Actonel for the treatment of osteoporosis. In 1999, Hoechst Marion Roussel merged with Rhone Poulenc Rorer to form Aventis. Since that time, the two participants in ABBH in the UK had been Procter & Gamble Pharmaceuticals and Aventis Pharma Limited. During that time Sanofi-Synthelabo Limited was the UK subsidiary of Sanofi-Synthelabo, an independent pharmaceutical company. It was only in the first quarter of 2005 that Sanofi-Synthelabo's operations were merged with those of Aventis.

In October 2006, the Authority wrote to Procter & Gamble, regarding an anonymous complaint received in relation to a nurse audit programme, run by ABBH between 2002 and 2004. The letter from the Authority stated a current employee at Sanofi-Aventis had complained under the Code regarding the ABBH nurse audit programme using a pseudonym. An anonymised copy of the letter of complaint was enclosed with the letter from the Authority, together with various documents provided by the anonymous complainant. (These documents in fact related to two separate audit programmes, the nurse audit programme and TOPCAT, which were described below).

Procter & Gamble noted that the complainant subsequently sent a second letter to the Authority making further allegations in respect of activities by ABBH. The Panel had ruled no breach of the Code regarding these latter allegations.

Investigation of the complaint by Procter & Gamble

Procter & Gamble stated that both it and Sanofi-Aventis experienced substantial difficulties investigating the matters raised by the anonymous complainant as the programmes had concluded and between 2 and 5 years had elapsed following the matters which were the subject of the complaint and some 2 years since the conclusion of the programmes referred to. During this period, staff at the company had changed and many of the people who participated in the programme were no longer with the company. Furthermore, a fire had taken place at the company's archive in July 2006 and substantial quantities of the

company's documents were destroyed. The information available to Procter & Gamble in relation to issues raised by the anonymous complainant had therefore been incomplete and the company's ability to investigate the allegations raised had been limited as a result of staff departures and the loss of documentation as a result of events outside the control of the company.

Procter & Gamble noted that the documentation provided by the anonymous complainant related to two programmes run by the ABBH; a nurse audit programme and TOPCAT, both of which reflected government policy to improve the diagnosis and management of patients with osteoporosis. The importance of this therapeutic area was emphasised in 1999 in the Secretary of State for Health's White Paper 'Saving Lives: Our Healthier Nation' which highlighted the significance of osteoporosis as a major cause of death and disability in older people. In the National Service Framework for Older People, issued in March 2001, Standard 6 focused on reducing the number of falls which resulted in serious injury. One of the key aspects of a strategy to reduce injury associated with falls was for GPs to take responsibility for assessing risk of osteoporosis and identifying those who required prevention or treatment. However, despite the importance placed upon the appropriate treatment of patients at risk of osteoporosis, at the time relevant to the complaint, doctors were under-resourced to make such diagnoses. In particular, the availability of DXA to measure bone mineral density and predict fracture risk, was severely limited. In the absence of DXA scanning, doctors at that time, were unable to diagnose patients at risk of osteoporosis.

In these circumstances, the programmes offered by Procter & Gamble and Sanofi-Aventis provided a valuable service to medicine and the NHS and substantial benefits to patients. In this regard Procter & Gamble referred to the statement of a GP and other doctors who participated in the programme. Similar services were provided at the time by other companies which supplied treatments for osteoporosis in the UK.

Nurse audit programme

As indicated above, Procter & Gamble submitted that the nurse audit programme was run by an independent organisation which specialised in providing audit protocols and reports for general practices. The programme followed a detailed protocol, incorporating best practice guidelines, including Primary Care Rheumatology guidelines and guidelines issued by the RCP. An explanation of the nurse audit programme was provided in the statement from a Procter & Gamble employee and supported by the email from a research nurse in clinical gerontology.

Procter & Gamble submitted that the programme was run in two phases. During phase 1, patients with established osteoporosis and/or a high risk of fracture (including patients on long term oral steroids, patients with confirmed osteoporosis on calcium supplements alone, patients with radiographic evidence of bone loss or vertebral deformity, etc and patients with a previous fragility fracture) would be assessed by the nurses as requiring immediate treatment. In phase 2, patients with osteoporosis risk factors but with an unconfirmed diagnosis, would be invited for DXA scanning and consultation with nurses. Following the review, the nurse would provide the GP with a final report of information collated from the records and patient reviews. The GP would then decide which treatment, if any, should be offered to patients with osteoporosis.

Procter & Gamble submitted that the involvement of ABBH representatives was limited to an initial discussion regarding the availability of the service in a non-promotional call to practices. This non-promotional call was preceded by and wholly separate from a standard promotional visit, at which representatives would seek to sell Actonel in the usual way. The nurse audit programme commenced as a pilot service in late 2001 and was discontinued on 31 October 2004.

TOPCAT

Procter & Gamble submitted that the TOPCAT programme also aimed to assist GPs to identify patients at risk of osteoporosis, but used software rather than nurses to analyse patients' records. The programme was applied by the GP or by an independent organisation. An explanation of the TOPCAT programme was provided in the statement of another Procter & Gamble employee.

Procter & Gamble submitted that the third party staff or the GP would use the TOPCAT software to identify patients at risk of osteoporosis. A patient so identified would be reviewed by the GP who would agree a management strategy for that patient, which might include further investigation or clinical review, advice regarding smoking cessation, prescription of vitamin D or other osteoporosis treatments.

Again, the involvement of ABBH representatives was limited to an initial discussion, during the course of a non-promotional visit, regarding the availability of the service.

Grounds for appeal

Procter & Gamble submitted that a feature of this complaint was the fact that the name of the complainant was not made known to the Authority, which was provided only with a pseudonym. While the complainant claimed to be a current employee of Sanofi-Aventis, although one who did not work in the osteoporosis part of the business, it was unclear whether the Authority had been able to confirm these details, or the source of the documents provided by the complainant in relation to the ABBH Nurse Audit and TOPCAT programmes.

Procter & Gamble submitted that furthermore, the Panel had seemingly relied upon the unsubstantiated evidence of the anonymous complainant in concluding that documents provided by the complainant, specifically the Nurse Audits document (ref CP&S UK MDO) and the TOPCAT Briefing Document (ref ACT8070904), the flowchart for selection of TOPCAT

surgeries (ref ACT7330504 A2541) and the TOPCAT Surgery Nomination Form (ref ACT7330504 A2541) were used to brief representatives in relation to the nurse audit or TOPCAT programmes. The explanations provided by Procter & Gamble and Sanofi-Aventis, as to why they believed such documents were not used to implement the programmes, had not been addressed by the Panel.

Procter & Gamble submitted that the explanations it provided were supported by evidence:

- Witnesses (including a Procter & Gamble employee who contributed to the development of the nurse audit programme; a Procter & Gamble employee who was involved in the running of the TOPCAT programme; doctors who reviewed and participated in the programmes; and a technician who carried out DXA scanning as part of the nurse audit).

- Sales data confirming the prescribing patterns of the practices which participated in the programmes.

- The explanations of the companies as to how the documents relied upon by the Panel should properly be interpreted.

In the context of this evidence, Procter & Gamble submitted that it was simply not open to the Panel to rely upon unsubstantiated inference based on an anonymous complaint that might not be tested through cross examination. Procter & Gamble provided an opinion from a QC in relation to these issues.

Procter & Gamble submitted that the Panel made various assertions which were unreasoned and unclear. Procter & Gamble had requested that proper explanations and/or reasons be provided in advance of the appeal hearing so that the company might consider the basis for the decision of the Panel and appropriately prepare its submissions for the appeal. However, the information requested had not yet been made available to the company.

Procter & Gamble noted that the Panel ruled a breach of Clause 18.1 by both Procter & Gamble and Sanofi-Aventis as a result of the findings that the selection of practices for the nurse audit and TOPCAT programmes indicated that 'representatives would only offer the services to those surgeries that agreed to use Actonel first choice/first line'. The Panel confirmed that the documents given to doctors in respect of the nurse audit and TOPCAT programmes did not refer to Actonel and were not objectionable. However, the Panel seemingly failed to recognise the very substantial benefits gained by patients and by the NHS as a result of the nurse audit and TOPCAT programmes. These benefits were clear from the statement by the Chairman of the National Osteoporosis Society Primary Care Forum who assisted in the development of the programmes that 'the audit service provided by ABBH has assisted practices to identify patients at risk of osteoporosis using [guidelines from the RCP and NICE]. The independent nurses and DXA scanning services have helped overcome the capacity issues facing the NHS'. This view was supported by the statements of the other doctors and of the technician who carried out the DXA scanning.

Procter & Gamble submitted that in reaching its conclusions with respect to Clause 18.1, the Panel relied on various documents provided by the complainant or disclosed by Procter & Gamble. However, reliance on these documents and their interpretation by the Panel was inappropriate.

Procter & Gamble submitted that the Nurse Audit document (ref CP&S UK MDO) was seemingly generated by Procter & Gamble in May 2004. A copy of the document was found by Procter & Gamble in a file containing draft documents and final material used for a sales conference in May 2004, although it did not appear that the document was used at the conference. In the context of the reference at the bottom of the document which indicated that it was created for the UK head office based commercial team - Customer Planning and Strategy, Procter & Gamble submitted that the document was used only for internal purposes at its head office (specifically to obtain the support of management to the continuation of the programme). In May 2004, the person responsible for the nurse audit programme at Procter & Gamble was no longer with the company. He was, at that time, subject to a performance review and his work was closely supervised. Any documents generated by him that was intended to be released to the sales force was first reviewed by his line manager who had confirmed that, prior to this investigation, she had not seen the Nurse Audit document. This evidence strongly suggested that the document was used only for internal purposes. Moreover there was no positive evidence that this document was used to brief representatives.

Procter & Gamble submitted that whilst the anonymous complainant had produced various documents in relation to the TOPCAT programme (a TOPCAT Briefing Document, a Flowchart for Selection of TOPCAT Surgeries and a TOPCAT Surgery Nomination Form) from an unidentified source, there was no evidence that any of this material was ever used to brief representatives or otherwise in implementing the programme.

Procter & Gamble submitted that the Panel had noted that it had provided no comments in relation to the TOPCAT Briefing Document (ACT 8070904), apparently supplied by the anonymous complainant. This was because the briefing document was not received by the team drafting the response. The reference on the document suggested that it was authorised by Aventis. Procter & Gamble had been unable to locate a copy among its records; it was therefore likely that any copy held by Procter & Gamble was destroyed in the fire. The document appeared to appropriately position the programme apart from the reference to 'Actonel First Line' which, as explained elsewhere, was inconsistent with the way the programme could be or was, in fact, run.

Procter & Gamble submitted that it had found the Programme: Update and Changes to Osteoporosis Review' document among its documents. In its ruling,

the Panel referred to the sentence in that document that 'assessment of the surgeries already reviewed showed there to be an increased proportion of patients already receiving bisphosphonate treatment compared to the pilot. This reduced the number of patients in each surgery that could benefit from the review. Therefore the quality of nominations needed to improve'. The Panel did not explain the apparently adverse inference it had drawn from this wording and Procter & Gamble was therefore prejudiced in its ability to respond. However, in circumstances where the aim of the nurse audit programme was to identify and investigate women at risk of osteoporosis, where the diagnosis was unrecognised, it was self evident that an increase in the proportion of patients taking bisphosphonates would indicate a higher proportion of patients already reviewed by the GP and a smaller number who would therefore benefit from the audit. In the context of a limited budget it was clearly appropriate for the programme to be directed towards practices where the greatest number of patients might benefit and, in these circumstances, no adverse inferences should be drawn from the wording of the document. Procter & Gamble referred to the background information to this document provided by the statement of one of its employees.

Procter & Gamble noted that the Panel subsequently referred to the 'Sales Force Call Agenda' (June 2003) also located by Procter & Gamble. The Panel asserted that this document 'clearly linked the offer of the service to those practices who agreed to prescribe Actonel first choice'. This interpretation of the document was incorrect. The agenda envisaged that a sales call would be undertaken where the objective was to 'gain agreement to prescribe Actonel as first choice therapy…'. However, there was no link made in the agenda between that sales call and the subsequent assessment of suitability for osteoporosis review. The list of factors to be considered in relation to the assessment of suitability for participation in the nurse audit, as set out in the agenda, did not include any requirement that the practice had in fact agreed to prescribe Actonel as first choice therapy or at all. Furthermore, it was significant that the Osteoporosis Surgery Booking Form also provided to the Authority included no requirement that the practice had agreed to prescribe Actonel first line. In these circumstances, Procter & Gamble submitted that the inferences drawn from the documents by the Panel were unfair.

Procter & Gamble submitted that the Panel had been wrong to conclude that the nurse audit and TOPCAT programmes were offered only to those surgeries that agreed to use Actonel first line. In fact, practices which did not prescribe Actonel first line were also nominated and did participate in the programmes. Sanofi-Aventis had provided the Authority with a statement from a GP who confirmed that this was the case and this had been reiterated by that GP and by other doctors who participated in the programme .

Furthermore, Procter & Gamble had obtained data in relation to the prescription of bisphosphonates by practices which participated in the nurse audit programme. Procter & Gamble's submission regarding this data was similar to Sanofi-Aventis.

Procter & Gamble submitted that data clearly demonstrated that neither the nurse audit programme nor the TOPCAT programme imposed a requirement that Actonel should be prescribed first line before practices could be nominated for inclusion. The data for individual practices did not support a contention that the nurse audit and TOPCAT programmes acted as an inducement to prescribe Actonel. The Panel had relied upon data provided by Procter & Gamble, which showed that 88% of treated patients were initiated on Actonel in the nurse audit programme between March 2003 and October 2004 and that approximately 60 patients were started on Actonel as a result of TOPCAT in 2004, in reaching its conclusion that the programmes did not meet the requirements of Clause 18.1 of the 2003 Code.

Procter & Gamble submitted that firstly, the 88% figure previously referred to was not credible. The data which formed the basis for this figure was not available to Procter & Gamble and it was wholly inconsistent with the sales data. In these circumstances and in the context of the sales data, the figure of 88% was more likely to refer to the number of patients prescribed a bisphosphonate, rather than the number prescribed Actonel.

Procter & Gamble submitted that the nurse audit and TOPCAT programmes must be considered in the context of the 2003 Code. While the evidence demonstrated clearly that practices were not selected for inclusion in the nurse audit and TOPCAT programmes only if they were willing to prescribe Actonel, even if the Appeal Board were to make a contrary finding, Procter & Gamble and Sanofi-Aventis submitted that this did not constitute a breach of Clause 18.1 of the 2003 Code.

Procter & Gamble noted that the supplementary information to Clause 18.1 of the 2003 Code stated that this 'does not prevent the provision of medical and educational goods and services which will enhance patient care or benefit the National Health Service'. Such services were welcomed by the Government and by the NHS and the Panel did not suggest they were objectionable. It was quite clear that the nurse audit and TOPCAT programmes provided a valuable service to the NHS in circumstances where the resources to identify patients at risk of osteoporosis, through DXA scanning, were limited and that patients derived substantial benefit from these programmes. However, it was self evident that services to medicine would not be provided by companies if the result was to benefit their competitors at their own expense. The result of the Panel's approach was that such programmes would be offered only by companies whose products had a majority market share, where the programme would not advantage their competitors. This was clearly undesirable.

Procter & Gamble noted that the supplementary information to Clause 18.1 of the 2003 Code went on to state '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…'. Extensive guidance was provided to assist companies in relation to medical and educational goods and services. It was noteworthy that at no place did the Code or its supplementary information suggest that the provision of medical goods and services might not be made available to practices that already prescribed a company's products, in circumstances where the doctor was free to prescribe any medication or no medication, as he saw fit. The revisions to the Code introduced in 2006 included no such wording.

Procter & Gamble submitted that if, in the circumstances described above, the Authority considered that services to medicine offered by a company to practices who were willing to consider prescribing that company's products, constituted a breach of Clause 18.1, this view should be clearly stated in the supplementary information. In the absence of any guidance indicating that such arrangements were objectionable it was unfair for the Panel to give a ruling adverse to Procter & Gamble and Sanofi-Aventis in circumstances where the programmes themselves were valuable and created no obligations for a participating doctor to prescribe Actonel or any medicine.

In summary Procter & Gamble submitted therefore the overwhelming weight of the evidence indicated that the nurse audit and TOPCAT programmes were provided as services to medicine, to fulfil clinical need and to benefit patients in the NHS. Practices which did not prescribe Actonel first line were not excluded from the programmes and there was absolutely no evidence that these programmes in any way constituted an inducement to prescribe, contrary to Clause 18.1.

Procter & Gamble submitted that a finding of a breach of Clause 18.1 did not necessarily result in a ruling of a breach of Clause 2. However, in this case, the Panel had provided no reasoning to justify the finding of a breach of Clause 2 in respect of both companies, simply stating that 'the overall arrangements brought discredit upon the pharmaceutical industry'. Procter & Gamble emphatically disagreed that this was the case. The supplementary information to Clause 2 stated 'a ruling of a breach of this clause is a sign of particular censure and is reserved for such circumstances'. In these circumstances, it was incumbent upon the Panel to provide proper reasons explaining the circumstances of this case that warranted such censure.

Procter & Gamble submitted that it was significant that, in reaching its conclusion with respect to Clause 2, the Panel had seemingly failed to take into account the following issues which should properly have been considered:

- The very substantial benefits both to patients and to the NHS resulting from the programmes and the fact that participating doctors were clearly free to prescribe whatever medicine they chose or to prescribe no treatment. In direct contrast to the conclusion of the Panel, a GP stated 'this kind of service represents true partnership between the NHS and pharmaceutical industry'.

- The fact that the Panel confirmed that the documents given to doctors with respect to the nurse audit and TOPCAT programmes were not objectionable.

- The fact that physicians did not perceive the programmes as inducements to prescribe. Statements provided by doctors who participated in the programmes had confirmed that they did not consider the arrangements an inducement to prescribe and that they would not have participated in the programme had they found any such inducement to be present.

- Clause 18.1 of the 2003 Code did not specifically exclude the offer of a service to medicine to those practices which already prescribed a company's products. (The 2006 version of the Code made no revision to incorporate such a requirement).

Overall, therefore, Procter & Gamble submitted that the ruling of the Panel in relation to both Procter & Gamble and Sanofi-Aventis, with respect to the nurse audit and TOPCAT programmes, was unreliable and unfair and it respectfully requested that the Panel's rulings in respect of breaches of Clauses 18.1 and 2 of the 2003 Code, were set aside by the Appeal Board.

Cases AUTH/1902/10/06 and AUTH/1903/10/06

COMMENTS FROM THE COMPLAINANT ON THE INITIAL SUBMISSIONS BY THE RESPONDENTS

The complainant noted that both companies stated their reasons for appeal as that the programmes offered much needed services to the NHS which otherwise would not be available. The complainant stated that this might or might not be true dependent on the locality served, however, in general access to NHS diagnostic services in osteoporosis was limited at the time of the programmes.

The complainant noted that an independent agency supplied and oversaw the audit and patient contact undertaken by nurses working to accepted professional standards. However, the complainant's view was that practices were selected by representatives on the basis of prescribing behaviour.

The complainant noted that practitioners were free to prescribe whatever they choose. The complainant alleged that the practices were selected on the basis that Actonel was their medicine of choice, accordingly, the GPs were at liberty to prescribe their medicine of choice ie Actonel, as borne out by 88% of bisphosphonate patients treated as a result of the nurse audit programme being treated with Actonel (data supplied to the Authority by the ABBH).

The complainant alleged that the documents provided with his complaint demonstrated that the programmes did breach Clause 18.1.

The complainant noted that Clause 2 breaches as a result of very similar breaches of Clause 18.1 as

reported in the November 2006 Code of Practice Review were ruled against two other major pharmaceutical companies for practically identical issues with sponsored patient identification programmes. Accordingly, if the Authority was to issue consistent rulings and subsequent sanctions then the current cases must represent a breach of Clause 2 and had unquestionably brought discredit upon the industry.

With regard to Sanofi-Aventis' submission that its current senior management team was not responsible for the conduct of these programmes, the complainant stated that this case was not being brought against individuals but against companies. Sanofi-Aventis represented the merger of Sanofi and Aventis and therefore must be held to account for this behaviour. If not, did a merger provide a means of terminating responsibility for inappropriate behaviour of legacy companies? Furthermore, it should be self-evident that employees responsible for implementing these programmes in a non-Code compliant fashion remained current employees of Sanofi-Aventis. Therefore, their current employer must be held to account for those historical transgressions.

The complainant was stunned and profoundly disappointed at the respondents' denials in this matter. It was utterly self-evident that the Nurse Audits document (ref CP&S UK MDO) document and the TOPCAT flowchart, Surgery Nomination Form and Briefing Document were all intended for a target audience of representatives. To state otherwise defied logic and was a truly pathetic attempt to deny the lack of Code compliance of these programmes. The complainant reminded the Appeal Board of the following:

Nurse Audits document (ref CP&S UK MDO):

- Objective section – 'To increase RSA sales by identifying new patients in Actonel friendly surgeries. To identify, evaluate and optimise treatment in … Actonel friendly surgeries. To increase Actonel new patient share post audit in surgeries'.
- Business return section - The complainant alleged that it was evident that this was completely unacceptable.
- Description section – 'We identify Actonel friendly surgeries and nominate to …'.
- Process section – '(2) Identify Actonel first line surgery, (5) Ensure all GPs would choose Actonel, (7) Monitor progress and watch sales increase'.

TOPCAT documents:

- Flowchart for selection of TOPCAT surgeries - Ensure all GPs are first line (if no, 'Rectify issues'). Also 'Profile chemists and other practice staff for information on progress and products used'.
- TOPCAT Surgery Nomination Form - Checklist section: 'Surgery preferred bisphosphonate therapy for all licensed indications is Actonel'. Also in the Project Review section on the back of the form - 'Patients prescribed Actonel % and number and Extra sales - RSA'.
- TOPCAT Briefing Documents - Point 1.1 and the rest of the document made repeated reference to your practices. Also point 1.3 stated 'It (TOPCAT) is for use with computerised practices: (a) where Actonel is first line'. Also point 1.6 highlighted that TOPCAT was complementary to the … nurse audit programme.
- Point 2 stated 'What can it deliver to you in sales'.
- Point 3 stated 'How do I sell TOPCAT to GP practices'.

The complainant alleged that for either company to deny the nature and purpose of these representative briefing documents beggared belief. Any member of the Appeal Board that had worked in the commercial section of the UK pharmaceutical industry for longer than 6 months would clearly see these documents for what they were. More importantly, these documents were sourced from representatives working within the ABBH for both Aventis and Procter & Gamble that had participated in implementing these programmes.

The complainant alleged that it was this final point that was the most alarming of this entire case. The companies had been caught red-handed for unethical practice - the most sensible thing to have done in this circumstance would have been to have raised their metaphorical hands and accept due sanction. The foundationless nature of the grounds for appeal were an act of utter desperation. However, such reprehensible misleading of the Authority should not go unpunished. The severest of sanctions at the Board's disposal should be considered as a result of this unethical appeal as the ABBH had attempted to undermine the credibility and operational effectiveness of the Authority to self-regulate.

The complainant was stunned at the companies' suggestion that the briefing documents in question were not provided to sales staff and perhaps merely served as 'positioning documents' for head office staff. Perhaps a reminder needed to be made that the Code applied to all activities and staff of a pharmaceutical company and was not limited in scope and application to field-based employees. Furthermore, and far more importantly, this defence was a blatant lie. The complainant unequivocally assured the Authority that the documents were sourced independently from several members of the ABBH field-based sales force, for further clarity, from employees of both companies (the complainant did not bring these allegations to bear lightly, without extensive evidence gathering and so without absolute certainty that a case needed to be answered). To suggest to the contrary beggared belief. In this regard, the complainant was pleased that the Panel had noted the following:

- The Nurse Audits document (ref CP&S UK MDO) bottom text box 'For more information - Please contact your RBM (regional business manager) for further information and details of the local nurse areas'. Furthermore, the same document's 'Business Return' section stated 'Increase of your sales of £9171.70 for each practice nominated over the first year' - who on Earth do the respondents suppose the word 'your' referred to in this sentence?! Obviously, the 'yours' in question were members of

the sales force responsible for introducing the programme to 'their' surgeries. Head office staff did not report to regional business managers as anyone having worked in commercial pharma would know.

- The TOPCAT Briefing Document repeatedly used the word 'your practices' and provided a sales story … why would this be provided to anyone other than a representative? The complainant suggested that the Authority contact the named individual who would be able to advise the Appeal Board which employees would make contact regarding these programmes ie sales force or head office staff and which functions received the briefing documents.

Additional points for the Appeal Board to consider:

- To state the obvious, Sanofi-Aventis represented the product of a merger between Sanofi and Aventis. The notion that a case should not be brought against Sanofi-Aventis because it represented a separate legal entity relative to its two prior constituents' elements was utterly specious. It might be unfortunate for Sanofi-Aventis to be tarnished by these historical events, but this was hardly ancient history and so the legacy of this reprehensible behaviour lay at the doors of both Procter & Gamble and Sanofi-Aventis.

- An email asking the sales forces to complete the SOP online training dated February 2004 indicated that the entire field force was still involved and was in conflict with the suggestion in the companies' response that the project was being wound down as of the fourth quarter of 2003.

In relation to the testimonial regarding the value and probity of the programme from a GP with a specialist interest in osteoporosis, was the GP shown the materials submitted with the complaint prior to writing this testimonial to inform him of the nature of the issue with this programme? If not, respectfully, this testimonial was of no significance and should not be considered as credible or relevant by the Appeal Board.

- An email from a Procter & Gamble employee dated 7 November 2001 stated one criteria of the pilot work to be the consideration of the 'Current bisphosphonate of choice' - this email suggested a relationship between service provision and prescribing behaviour.

Furthermore, the NICE Technology Appraisal 87, Paragraphs 3.2, 3.3 and 3.4 included the following national shares of the bisphosphonate market in England for the period 2003/2004 and national case sales for this period:

Alendronate (Fosamax - MSD) £66M pa	61%
Etidronate (Didronel - P&G) £13.7M pa	23%
Risedronate (Actonel - ABBH) £16M pa.	16%

The complainant noted that the Authority had established from the ABBH that 351 practices nationally were involved during 2003/2004 serving patient populations of 2.2 million representing ~3.8% of the UK population. Furthermore, of 28,280 patients screened, 16,759 were treated with any medicine of which 15,046 were treated with Actonel. Accordingly 88% of treated patients were treated with Actonel; 88% versus a national market share during the same period of 16% was such a disparity on a programme of such scale. Or did this data serve to unequivocally support the crux of the complainant's allegations which were supported by documentation obtained from ABBH sales force members during 2006 (which remarkably seemed extraordinary difficult for the companies to source themselves in the course of this complaint on account of fires, mergers and IT updates)?

The complainant alleged that the documents he provided to the Authority in combination with the materials presented by the companies and the enormous disparity between national and ABBH programme prescribing habits illustrated that the Panel was correct to rule breaches of Clause 18.1 and 2. On these grounds the appeal should be rejected, and the matter be referred to the ABPI Board of Management for consideration of further sanctions on account of the utterly inappropriate attempts undertaken by the ABBH in the course of this appeal.

COMMENTS FROM THE COMPLAINANT ON THE FURTHER SUBMISSIONS BY THE RESPONDENTS

The complainant commented upon the documents from Procter & Gamble firstly, and where not duplicated added additional comments regarding the Sanofi-Aventis documents.

The complainant's first point was that he was a current employee of Sanofi-Aventis in the UK. The conduct of the complainant's employer in the course of this case had illustrated precisely why this case needed to be raised anonymously. Accordingly, to protect his identity and the identity of individuals that had provided documents and insight regarding the conduct of the programmes in question the complainant must remain anonymous.

The complainant alleged that the submission from Procter & Gamble that the Panel had relied upon documents that were never used to implement the nurse audit or TOPCAT programmes was categorically untrue. The documents provided to the Authority were sourced from a member of the ABBH sales team responsible for implementation of this programme (employed by Sanofi-Aventis to be precise). The complainant subsequently discussed the conduct and operational procedures of the programmes with a number of individuals employed in the ABBH sales force between 2002 and 2004 who all confirmed an unequivocal link between service provision and business metrics for Actonel within the target surgeries. Furthermore, all of the individuals, representing both member companies of the ABBH, confirmed that all members of the sales teams were absolutely clear that the programme was a very

important tool to drive Actonel sales.

The complainant stated that it was self-evident that he had obtained the materials from someone. Clearly, this was not a member of the marketing function.

The complainant stated that were his comments above not to reflect the facts of the case, the notion that documents acknowledged by both parties as having existed were acceptable as internal head office briefing documents was not consistent with the Code. Marketing teams must strictly adhere at all times to the letter and spirit of the Code and exceptions were not made for documents intended to persuade senior managers of the company to provide ongoing support to marketing led so-called service to medicine programmes.

Furthermore, the complainant alleged that the email of 7 November 2001 contradicted the claims of Procter & Gamble's employee that no link existed between service provision and prescribing behaviour:

'The pilot will run through November. In the meantime if any of you have any nominations of surgeries who you feel may be interested in participating in an osteoporosis audit please supply the following details to your RBM:
Surgery location
Patient practice size
Number of GPS
Current bisphosphonate of choice.

Please do not offer the service to our customers, simply gather information on interested parties in the event we scale up after the pilot.
Please direct all questions to myself.'

The complainant requested the Appeal Board to establish from Procter & Gamble why 'Current bisphosphonate of choice' was a required detail in relation to the pilot practices and how this did not constitute an evidential link between prescribing behaviour and provision of service as early as the pilot phase of the nurse audit programme.

In response to Procter & Gamble's submission that it believed the 88% figure referred to was not credible, the complainant noted that firstly this specific piece of data was provided by Procter & Gamble which stated from data provided from the nurse audit programme, from March 2003 to October 2004, 351 practices were audited, involving 2,203,612 patients. 28,280 patients were invited for screening by their GPs, of which 16,759 were treated with any therapy. 15,046 (53%) of screened patients were treated with risedronate (88% of all treated patients). Procter & Gamble also stated that from the TOPCAT programme, 72 practices were nominated for use of this audit tool in 2004, involving 272,322 patients. 2,956 patients were identified as being at risk of osteoporosis. Approximately 60 patients were initiated on Actonel in this timeframe.

The complainant had stated that his research had established that 424 practice based audits had taken place resulting in 17,532 patients receiving bisphosphonates, the vast majority of which being Actonel. This data was sourced from an individual employed within the ABBH sales team during 2002-2004. Combination of the data from Procter & Gamble for both the nurse audit and TOPCAT equated to 423 practice based audits and 15,106 patients on Actonel. Application of 88% market share of bisphosphonate treated patients to the number of bisphosphonate treated patients identified by the complainant's original research (ie 17,532) would equate to 15,428. Whilst circumstantial evidence, given that the complainant did not acquire copies of the materials documenting the number of audits and patients treated, the complainant hoped that the remarkably consistency of the numbers reported in the original complaint with that from Procter & Gamble provided the Appeal Board with further reassurance of the lengths to which the complainant had gone to, to ensure that a complaint needed to be answered before bringing this to the attention of the Authority.

The complainant referred to cases that were practically identical in nature to Cases AUTH/1902/10/06 and AUTH/1903/10/06 (Cases AUTH/1807/3/06, AUTH/1810/3/06 and AUTH/1814/3/06). In both cases breaches of Clause 2 in addition to Clause 18.1 were ruled. Accordingly, if the Authority was to issue consistent sanctions and the Clause 18.1 breach in the current case was upheld, a breach of Clause 2 was entirely appropriate.

The complainant noted the statement from the Procter & Gamble employee and made the following comments: 'I should say that there was, at no point in any of these materials, a suggestion that participation in the programme was linked to prescription of any medicine and no reference to risedronate at all'. The complainant referred the Appeal Board to another section where the employee failed to provide an explanation of the reference to current bisphosphonate of choice when selecting pilot practices in the email of 7 November 2001.

'Representatives were instructed to conduct a standard sales call to discuss use of risedronate for the treatment of osteoporosis. If the relevant doctor had previously prescribed risedronate to any of his patients or displayed some interest in prescribing risedronate, the representative would request a second non-promotional appointment to discuss the Nurse Audit Programme. (If a particular doctor indicated that, where a bisphosphonate was indicated, he would only prescribe a product manufactured by one of our competitors (eg Fosamax) and would not consider risedronate, then representatives would not routinely book a second appointment to discuss the Nurse Audit Programme. Nevertheless, this did not mean that practices who did not prescribe risedronate were excluded and some such practices did, in fact, participate in the Programme)'. The complainant alleged that this was a mis-representation of the protocol for briefing representatives. Regional sales managers would, during the primarily oral briefings discuss the TOPCAT Briefing Document, TOPCAT flowchart and the Nurse Audits document (ref CP&S UK MDO).

'If the relevant doctor had previously prescribed risedronate to any of his patients or displayed some interest in prescribing risedronate, the representative would request a second non-promotional call to discuss the Nurse Audit programme. (If a particular doctor indicated that, where a bisphosphonate was indicated, he would only prescribe a product manufactured by one of our competitors (eg Fosamax) and would not consider risedronate, then representatives would not routinely book a second appointment to discuss the Nurse Audit Programme)'. The complainant alleged that this statement confirmed that selection of the offer of an audit programme relied upon the doctor's prescribing habits. Whilst the doctor in the circumstance described above had not been requested to prescribe a particular medicine in return for provision of the service, the representative had linked service provision to business metrics by pre-selecting those surgeries to be offered the service as described in the statement. Furthermore, what guidance was offered to the representative when a GP that would not prescribe Actonel heard about the service from a colleague that did (and therefore had received the service) and asked the representative to place an audit in his surgery? The answer to this obtained from the complainant's contacts within the sales organisation was that the non-Actonel prescribing GP would be placed on a 'waiting list' and the representative recommended to steer clear of that particular surgery for a healthy interval.

'During the second call, the representative would discuss the Nurse Audit Programme and if the practice appeared one where the programme would be of use (eg because of the ages of patients served by that practice and the fact that a similar audit had not been conducted in the previous 2 years) and the GPs wished to participate, the representative would nominate the practice for approval. The level of risedronate prescribing was not a factor which determined whether a practice would be nominated. (This is confirmed by the list of factors included in the Sales Force Call Agenda under 'Assessment of Suitability for Osteoporosis Review') …. Details of approved practices were passed to the … nurses who would then initiate contact with the practices. From that stage, ABBH and the staff of its member companies had no further involvement in the Programme'. The complainant alleged that it was categorically untrue as described above.

'Such an approach (i.e. selection of first line surgeries only) would have been wholly unrealistic in the context of risedronate's limited market share'. The complainant stated that representatives were required to consider expressed prescribing behaviour for new patient episodes. At the time, <10% of osteoporotic patients were treated with any RCP endorsed therapies. Accordingly, the existing market was minimal and therefore the total market share was not the representatives' interest … the 'dynamic' or intended future prescribing behaviour would determine whether GPs would be offered the service. This of course might be known to the representative from their routine promotional calls on the GPs to whom they would introduce the service. Accordingly, how any call from a representative could be completely divorced from promotional agendas presented a larger question of the wisdom of Clause 18.1 in its current form.

'… from November 2003, … I had overall responsibility for marketing. I have therefore been asked to comment in relation to the … Nurse Audit Document (Ref CP&S UK MDO) which was seemingly generated by Procter & Gamble in May 2004. A copy of this document was found in a file containing draft documents and final material used for a sales conference in May 2004, although I do not believe the document was used at the conference. In May 2004, the person with responsibility for the Nurse Audit Programme at Procter & Gamble was an individual, who is no longer with the company. He was, at that time, subject to a performance review and his work was closely supervised. Any documentation generated by him that was intended to be released to the sales force would have been first reviewed by me as his line manager. However, prior to this investigation, I had not seen or been asked to review the … Nurse Audit Document. I am therefore confident that it was not used to brief representatives in relation to the … Programme'. This contention was flawed. The complainant repeated that the documents provided to the Authority were sourced from an ABBH sales team member and familiar to several other sales team members at both Sanofi-Aventis and Procter & Gamble.

The complainant alleged that a statement from a second Procter & Gamble employee, 'The second non-promotional call was not routinely requested if a particular doctor indicated that, where a bisphosphonate was indicated, he would only ever prescribe a product manufactured by one of our competitors (e.g. Fosamax) and would never consider risedronate' as above, confirmed a selective link between provision of the service in question and prescribing behaviour. The purpose of the second non-promotional call was to separate sales activity from service provision … accordingly, the representative should not determine whether the second non-promotional call took place at all on the basis of the GP's prescribing behaviour.

With regard to Sanofi-Aventis' submission the complainant stated that the first issue with a doctor's submission was whether he had been fully informed of the documents provided to the Authority that had formed the basis of this complaint. If not, he had not been transparently informed of the issue with the ABBH programmes. There was no question that the service was beneficial to GPs and their patients, particularly so in areas lacking NHS diagnostic and assessment infra-structure. That was an entirely separate point to the issue of Code compliance of the programme from the perspective of an inappropriate linkage of service to prescribing behaviour.

Furthermore, respectfully, the relevance of this testimonial should be measured in light of the doctor's acknowledgment that: 'Several years had elapsed since the Programme was concluded and I now had little recollection of its details'.

The complainant was very disappointed that he felt unable to attend the appeal hearing for fear of diminishing his future employability in the pharmaceutical industry. Like many of his colleagues, the complainant considered that the UK pharmaceutical industry was sitting on a precipice in respect of its likelihood of maintaining the privilege to self-regulate its business practices. Decisive action must be taken against those whom would endanger self-regulation because the consequences of introducing a body such as the FSA in their sphere of business would be catastrophic for the collective reputations and make day-to-day business activities far more cumbersome than was currently the case. Therein laid the complainant's motivation to bring this case to bear. The last four months or so had been quite the worst of his professional life, however, the truth must be made apparent. The complainant sincerely hoped that the Appeal Board considered the evidence placed in front of it, rejected the appeal and ruled breaches of Clauses 18.1 and 2.

The complainant alleged that the conduct of the ABBH in the course of this appeal had almost rendered the actual case in hand a secondary issue. There could be no excuse for denial of the truth and mis-representation of the facts to the Authority. Sadly, the complainant hoped that the conduct of the ABBH in the course of these cases would result in the Appeal Board referring the case to the ABPI Board of Management. The ABPI could ill-afford in these difficult times to have member companies that demonstrated contempt for the letter and spirit of the Code; suspension if not expulsion might serve as an appropriate sanction that would focus minds across the industry on how the industry should conduct itself.

APPEAL BOARD RULING

The Appeal Board noted that the nurse audit, which ran from 2002 until 2004 was sponsored by the ABBH which comprised Procter & Gamble and Aventis. Aventis had since merged with Sanofi to become Sanofi-Aventis.

The Appeal Board noted that Clauses 2 and 18.1 of the 2003 Code were the same as Clauses 2 and 18.1 of the 2001 Code and thus considered the matter under the 2003 Code. The supplementary information to Clause 18.1 of the 2001 Code was the same as the supplementary information to Clause 18.1 of the 2003 Code ie that medical and educational goods and services which enhanced patient care or benefited the NHS could be provided within certain conditions.

The Appeal Board noted that the material for health professionals referred to the ABBH and bore a declaration of sponsorship which referred to Aventis and Procter & Gamble. Some material for internal use such as the Programme: Update and Changes to Osteoporosis Review document (ref A2121) provided by Procter & Gamble bore the names of each company but not the ABBH. A document Programme: RBM Responsibilities (June 2003) also bore the reference number A2121 and mentioned the Alliance.

The Appeal Board noted that osteoporosis was a serious disease and that a service which would increase diagnosis and treatment would be of benefit to patients. Nonetheless any such service had to comply with the Code.

The Appeal Board was concerned about the limited documentation provided by the companies. It noted the companies' explanations in this regard. In relation to the material provided by the complainant the Appeal Board noted that whilst it was possible to contact the complainant his identity was unknown and thus it was extremely cautious when deciding what weight, if any to attach to his evidence.

The Appeal Board noted the detailed comments provided by all the parties. It also noted with concern the changes in submission by Procter & Gamble with regard to its initial acceptance of a breach of Clause 18.1 and its subsequent submission that it only accepted a breach of Clause 14 in relation to its failure to certify representatives' briefing material. It also noted that Procter & Gamble had decided that its statement that 88% of treated patients were initiated on Actonel was not true; the figure of 88% had been incorrectly calculated.

The Appeal Board noted that the parties' submissions differed. Nonetheless there were some similarities between them. The complainant had provided documents which he stated were intended to be used by representatives; Sanofi-Aventis and Procter & Gamble disagreed and stated that the documents had not been used in the field. The Appeal Board examined the sales data submitted by the companies but did not consider that such data could ever be used to demonstrate that sales staff had been appropriately briefed. The Appeal Board ultimately concentrated on two documents regarding the nurse audit which both companies agreed had been used by sales personnel; a document headed 'Actonel GP Call Agenda and Follow Up November 02 to January 03' and the Sales Force Call Agenda (June 2003) (ref A2121).

'The Actonel GP Call Agenda and Follow Up' appeared to set out the sequence of events from a sales call to an audit call. The first instruction was 'Call objective 1: Gain agreement to Rx [prescribe] Actonel as 1st choice therapy for patients with low BMD [bone mineral density], [corticosteroid induced osteoporosis], patients with previous fragility fracture'. If the call objective was not achieved then representatives were given a second call objective of 'If dosing were not an issue Gain agreement to proactively Rx Actonel 1st line for [the same group of patients]'. If the answer was still no then representatives were to do the second product detail. Conversely if call objective 1 or 2 was achieved the next step was referred to as Step 1 of the Audit call which was to 'Book another appointment with the GP with a profile objective: To gain a full understanding of GP's level of interest and commitment to conducting an osteoporosis review in the practice … WITHOUT ACTUALLY OFFERING THE [nurse audit] SERVICE'. Having done that the representative then had to book an appointment with the most influential GPs in the practice to ensure that they supported an osteoporosis

review. The Appeal Board considered that the document was in effect briefing material which instructed representatives how to offer the service. It appeared that representatives would not offer the service until they were sure that the doctors in the practice supported an osteoporosis review and would, as part of that review process, prescribe Actonel as either first choice or first line therapy to suitable patients. The Sales Force Call Agenda (June 2003) similarly showed that a doctor's agreement to prescribe Actonel as first choice therapy was the first hurdle to being offered the service. This document also included an assessment of suitability for osteoporosis review which included a cut off of a total patient population above 3,000 for the audit service to be offered.

The Appeal Board considered that companies had to be clear and unambiguous when instructing representatives about their role in such matters. The Appeal Board considered that the link between the promotion of Actonel and the provision of the service including the selection of practices as described in the material was unacceptable. The Appeal Board did not accept the companies' submission that the two documents clearly separated the sales and non promotional calls. The Appeal Board considered that neither the content or layout of either document were satisfactory in this regard. The companies acknowledged that the layout of the documents was 'unfortunate'.

As an indication as to how the service was offered in practice, the Appeal Board noted a statement from one of Procter & Gamble's employees. The employee stated 'If a particular doctor indicated that, where a bisphosphonate was indicated, he would only prescribe a product manufactured by one of our competitors (eg Fosamax) and would not consider risedronate [Actonel], then representatives would not routinely book a second appointment to discuss the Nurse Audit Programme. Nevertheless, this does not mean that practices who did not prescribe risedronate were excluded and some such practices did, in fact, participate in the Programme'.

Notwithstanding the statement that some surgeries which did not prescribe Actonel were offered the service, the Appeal Board considered that the link in the representatives' material between the promised prescription of Actonel by the doctor and the subsequent offer of the service by the representative was unacceptable. It considered that the criteria for the selection of practices and the failure to adequately separate the promotional and non promotional role of the representatives was such that the arrangements failed to comply with the requirements of Clause 18.1.

The Appeal Board upheld the Panel's ruling of a breach of the Code. The appeal on this point was unsuccessful. The Appeal Board considered that the concerns about the material which gave rise to a breach of Clause 18.1 were so serious that they brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board upheld the Panel's ruling of a breach of Clause 2. The appeal on this point was unsuccessful.

The Appeal Board noted its comments above about the weight to be attached to the evidence. The Appeal Board considered that there was insufficient evidence to establish, on the balance of probabilities, whether the arrangements for the TOPCAT service complied with the Code. The Panel's ruling in this regard no longer stood. Accordingly, there was no breach of the Code in relation to arrangements for the TOPCAT service.

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 breaches of the Code in relation to the nurse audit programme. The Appeal Board was concerned about the paucity of documentation provided by both companies in all circumstances. The Appeal Board decided, in accordance with Paragraph 11.3 of the Constitution and Procedure, to require an audit of both companies' procedures in relation to the Code to include an examination of policies and procedures relating to the ABBH. On receipt of the audit reports the Appeal Board would decide if any further action was required.

Upon receipt of the audit report of Sanofi-Aventis, the Appeal Board decided that on the basis that the recommendations were implemented no further action was required.

Upon receipt of the audit report of Procter & Gamble, the Appeal Board considered that there was much work still to be completed to implement the recommendations and it was concerned about the inadequacy of the certification arrangements. The Appeal Board decided that Procter & Gamble should be re-audited in January 2008.

Complaint received	**19 October 2006**
Undertakings received	
Case AUTH/1902/10/06	**23 May 2007**
Case AUTH/1903/10/06	**24 May 2007**
Report to the Appeal Board	**19 April 2007**

CASES AUTH/1971/3/07 and AUTH/1972/3/0

SERVIER LABORATORIES v ROCHE and GLAXOSMITHKLINE

Promotion of Bonviva

Servier Laboratories alleged that a leavepiece and a journal advertisement for Bonviva (ibandronic acid), issued by Roche and GlaxoSmithKline, were, *inter alia*, misleading. Both pieces featured the claim 'Building bones' which Servier considered, in the context of promotion of a medicine licensed to treat osteoporosis, implied it had a positive action on bone formation, a bone-forming effect; a doctor would assume that Bonviva was a medicine which positively encouraged growth of bone and not one which might prevent further deterioration of osteoporotic bone. Servier noted that Bonviva, a biophosphonate, actually had a negative impact on bone formation and could not therefore be considered to be 'building bones'.

The summary of product characteristics (SPC) for Bonviva 150mg stated that it acted selectively on bone tissue and specifically inhibited osteoclast activity without directly affecting bone formation. Rodan *et al* (1996) stated that regarding the mechanism of action of bisphosphonates 'there is a reduction in bone turnover', 'evidenced by a decrease in both bone resorption and bone formation'. Furthermore the authors stated that 'besides resorption, formation is decreased too, as evidenced by a reduction in the bone formation surface'.

Servier thus considered that 'building bones' was not an appropriate term to describe a treatment which stopped bone resorption as well as reducing bone formation and as such it was inconsistent with the particulars listed in the Bonviva SPC, misleading and incapable of substantiation.

The Panel noted from the SPC that Bonviva acted selectively on bone tissue and specifically inhibited osteoclast formation (ie bone resorption) without directly affecting bone formation. Bonviva led to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women. Bonviva, however, did not build bone per se; its principal pharmacodynamic action was to inhibit bone resorption. The Panel noted that bone resorption and bone formation were coupled such that if bone resorption was decreased then bone formation was also decreased.

Delmas *et al* (2004) measured the biochemical markers of bone turnover in postmenopausal women with osteoporosis. Patients were randomized to receive placebo or Bonviva dosed either daily or intermittently. Both Bonviva regimens resulted in persistent levels of suppressed bone resorption (53-68%; p<0.0001 vs placebo) and bone formation (36-41% for serum osteocalcin; p<0.0001 vs placebo). The Panel noted that the biochemical markers showed that although bone resorption was suppressed rapidly (within 3 months), the markers for bone formation did not reach a plateau until within approximately 6 months' treatment. The delay in the decrease of the markers of bone formation compared with those of resorption could be explained by the normal coupling between formation and resorption, since bisphosphonates did not have a direct inhibitory effect on osteoblastic bone formation. The net reduction in bone turnover led to significant increases in spinal and hip BMD (p <0.0001 vs placebo) relative to baseline and a marked reduction in the incidence of vertebral fracture.

The Panel considered that although, as stated in the SPC, treatment with Bonviva led to progressive net gains in bone mass, such gains were not as a direct result of 'Building bones'. Increased bone mass was a result of a decrease in bone turnover with bone resorption being suppressed and then as a consequence of that, but not due to direct action of Bonviva, bone formation being suppressed to a lesser degree. In the Panel's view 'Building bones' implied that Bonviva had a positive effect on bone formation and that in some way it might stimulate osteoblasts which was not so. Any increase in bone mass, as a result of Bonviva therapy, was as a consequence of its main pharmacodynamic action, ie inhibition of bone resorption.

The Panel considered that 'Building bones' was a misleading claim which could not be substantiated; it implied that Bonviva had a direct bone-forming action which was not so. Breaches of the Code were ruled. This ruling was appealed.

Although noting its ruling above, the Panel did not consider that the claim was inconsistent with the Bonviva SPC which stated that therapy led to progressive net gains in bone mass. No breach of the Code was ruled in that regard.

Upon appeal by Roche and GlaxoSmithKline, the Appeal Board noted from its SPC that Bonviva acted selectively on bone tissue and specifically inhibited osteoclast formation (ie bone resorption) without directly affecting bone formation. Bonviva led to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.

The SPC did not refer to 'Building bones' although it

did state that treatment with Bonviva led to progressive net gains in bone mass. The patient information leaflet stated that 'Bonviva prevents loss of bone from osteoporosis, and helps to rebuild bone'. The Appeal Board considered that 'leads to progressive net gains in bone mass' and helping to rebuild bone described an indirect effect of therapy whereas 'Building bones' implied that Bonviva had a positive direct effect on new bone formation and that in some way it might stimulate osteoblasts which was not so. Any increase in bone mass, as a result of Bonviva therapy, was as a consequence of its main pharmacodynamic action, ie inhibition of bone resorption.

The Appeal Board noted the respondents' submissions regarding the net clinical effect of Bonviva but nonetheless considered, on balance, that 'Building bones' was a misleading claim which could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of the Code.

Servier Laboratories Ltd complained about the promotion of Bonviva (ibandronic acid) by Roche Products Limited and GlaxoSmithKline UK Ltd. The items at issue were a leavepiece (ref BON/LVP/06/25189/1) and an advertisement (ref BON/DPS/06/25931/2). Servier supplied Protelos (strontium ranelate). Bonviva and Protelos were both licensed for the treatment of postmenopausal osteoporosis.

COMPLAINT

Servier noted that both the leavepiece and the advertisement featured the claim 'Building bones'. Servier considered that 'Building bones', in the context of promotion of a medicine licensed to treat osteoporosis, implied it had a positive action on bone formation, a bone-forming effect; a doctor would assume that Bonviva was a medicine which positively encouraged growth of bone and not one which might prevent further deterioration of osteoporotic bone.

Servier noted that Bonviva, a bisphosphonate, actually had a negative impact on bone formation and could not therefore be considered to be 'building bones'.

The summary of product characteristics (SPC) for Bonviva 150mg stated that it belonged to the nitrogen-containing group of bisphosphonates, which acted selectively on bone tissue and specifically inhibited osteoclast activity without directly affecting bone formation. Rodan *et al* (1996) stated that regarding the mechanism of action of bisphosphonates 'there is a reduction in bone turnover', 'evidenced by a decrease in both bone resorption and bone formation'. Furthermore the authors stated that 'besides resorption, formation is decreased too, as evidenced by a reduction in the bone formation surface'.

Servier noted that Roche considered that the effect of increasing bone mass, which was observed with bisphosphonates justified the claim 'Building bones'. However Servier disagreed; increasing bone mass was not the same as 'building bones'. Bone mass could be increased by mechanisms other than increasing formation, for example, relating to the mechanism of action of bisphosphonates. Rodan *et al* stated that 'after the decrease in bone turnover... bone will have more time to complete mineralization…thus "older" bone has a higher mineral content'.

Roche had argued that referenced publications supported its claims, using phrases such as 'bone accrual' (Chesnut *et al*, 2004), 'formation of new bone of normal quality' (Müller *et al*, 2004, Lalla *et al*, 1998, and Smith *et al* 2003) and 'bone gain' (Delmas *et al*, 2004). Servier believed that this response was in line with its belief that 'building bones' implied increasing bone formation. However, inspection of these papers revealed that none of the phrases quoted above were used within the papers and furthermore none would support Bonviva being associated with increased bone formation.

For the reasons outlined above, Servier considered that 'Building bones' was not an appropriate term to describe a treatment which stopped bone resorption as well as reducing bone formation and as such it was inconsistent with the particulars listed in the Bonviva SPC, misleading and incapable of substantiation, in breach of Clauses 3.2, 7.2 and 7.4 of the Code.

RESPONSE

Roche responded on behalf of itself and GlaxoSmithKline. Roche stated that the claim 'Building bones' was not used in isolation but as part of a longer statement. On the leavepiece it appeared as 'Building bones with one tablet, once a month' and in the advertisement it formed part of the claim 'Building bones, month, after month, after month'. The basis for these claims, and in particular references to 'Building bones', was consistent with the Bonviva SPC. It was also supported by a body of peer reviewed evidence.

To explain the rationale for the use of the claim 'Building bones' it was useful to understand the currently accepted mechanism of action of bisphosphonates. It was also pertinent to clarify the difference between direct bone formation and the process of building bone which might be either a direct or indirect consequence depending on the agent's mechanism of action. It was also useful to place this in the context of the overall aim of therapy, which was to reduce the risk of postmenopausal osteoporotic fracture. Section 5.1 of the Bonviva SPC stated under the heading 'Mechanism of action':

> 'Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation. It does not interfere with osteoclast recruitment. Ibandronic acid leads to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.'

Roche noted in particular the statement that 'Ibandronic

acid leads to progressive net gains in bone mass.' It was clear that increasing bone mass required the addition of bone to the existing skeleton and this action was effectively 'Building bones'. This was manifested as a demonstrable increase in bone mineral density (BMD) that was significant both statistically and clinically with regard to its resultant effect on fracture rates.

The SPC was based on the balance of evidence and could not be considered misleading. It reflected the current evidence base and understanding of how bisphosphonates worked and therefore reduced fracture risk in postmenopausal osteoporosis.

The mechanism by which bisphosphonates increased bone mineral density was an indirect one via their inhibitory effect on osteoclasts. Roche noted Rodan *et al* stated that resorption and formation were decreased in the presence of bisphosphonates. However to take this statement alone would be to do so out of context and Rodan *et al* went on to state that 'the reduction in total bone formation surface is secondary to diminished resorption and reflects reduced remodelling'. Rodan *et al* further stated that 'there is no evidence for reduced osteoblastic activity'. The authors' conclusion was that 'the amount of bone formed at each individual basic multicellular unit (BMU) measured by the thickness of the newly formed bone, is not decreased but, if anything, even increased'.

When looking at Bonviva specific data it had been seen that in postmenopausal osteoporotic women treated with daily ibandronic acid (2.5mg), increments in lumbar and hip BMD were observed within 12 months. Bone accrual continued throughout the duration of treatment (Chesnut *et al*). Likewise, intermittent ibandronic acid, administered either as a monthly oral dose, or a quarterly intravenous dose, also induced gains in bone mass (Miller *et al* 2005 and Delmas 2006). These clinical observations were entirely consistent with the findings of preclinical studies which provided further clarification that ibandronic acid increased bone mass through the formation of new bone of normal quality with increased or equal mechanical strength (Müller *et al*, Lalla *et al* and Smith *et al*). This reflected the findings of Rodan *et al* stated above.

Roche acknowledged that the Bonviva SPC stated 'bisphosphonates…specifically inhibit osteoclast activity without directly affecting bone formation'. The key here was the statement 'directly affecting bone formation'. Roche did not suggest that Bonviva directly triggered osteoblastic action and therefore Bonviva was not a bone forming agent like Protelos. However as stated earlier it did effect bone turnover due to its influence on the coupling balance of bone formation and bone resorption. The fact that Bonviva treatment affected both bone formation and bone resorption was evident from the data (Delmas *et al*). These data also illustrated that the effect of upon bone resorption was greater than that upon bone formation. As Bonviva suppressed bone resorption to a greater extent than bone formation, the net effect was one of bone gain (Delmas *et al*). This was the mechanism by which BMD was increased. These data further substantiated the claim 'Building bone'.

Servier noted in its complaint that it was aware of these data, however, as was apparent in intercompany dialogue, it did not recognise that there was a distinction between direct anabolic bone formation and bone building which could be brought about by a number of mechanisms both direct and indirect. Roche considered that to only reserve the term 'Building bone' for directly acting bone forming agents was misleading as bisphosphonates had a huge impact on BMD and had, as highlighted above, been shown to increase bone mass through the formation of new bone of normal quality with increased or equal mechanical strength (Müller *et al*, Lalla *et al* and Smith *et al*).

It was this evidence base that resulted in the regulatory approved Bonviva patient information leaflet stating that 'Bonviva prevents loss of bone from osteoporosis, and helps to rebuild bone. Therefore Bonviva makes bone less likely to break'.

In summary, Bonviva reduced the risk of fracture in postmenopausal osteoporosis through its action on the balance between bone formation and bone resorption on the surface of the bone. This resulted in an increase in bone mass and thus indirectly Bonviva built bone. Roche therefore concluded that the claim 'Building bones' did not breach Clause 3.2, as it was consistent with the terms of the marketing authorization and was not inconsistent with the SPC. Neither did the statement breach Clause 7.2 nor 7.4 as the information was accurate, balanced, fair, objective and unambiguous and reflected the evidence relating to the action of ibandronic acid.

In the eyes of prescribers and patients the essential effect required was to increase BMD. Bisphosphonates, including Bonviva, had this effect. The mechanism was not relevant, and thus by demonstrating an increase in BMD, Roche was confident that the claim 'Building bone' was supportable and not in breach of Clauses 3.2, 7.2 and 7.4.

PANEL RULING

The Panel noted from the SPC that Bonviva acted selectively on bone tissue and specifically inhibited osteoclast formation (ie bone resorption) without directly affecting bone formation. Bonviva led to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women. Bonviva, however, did not build bone per se; its principal pharmacodynamic action was to inhibit bone resorption. The Panel noted that bone resorption and bone formation were coupled such that if bone resorption was decreased then bone formation was also decreased.

Delmas *et al* measured the biochemical markers of bone turnover in postmenopausal women with osteoporosis. Patients were randomized to receive placebo or Bonviva dosed either daily or intermittently. Both Bonviva regimens resulted in persistent levels of suppressed bone resorption (53-68%; $p<0.0001$ vs placebo) and bone formation (36-41% for serum osteocalcin; $p<0.0001$ vs placebo). The Panel noted that

the biochemical markers showed that although bone resorption was suppressed rapidly (within 3 months), the markers for bone formation did not reach a plateau until within approximately 6 months' treatment. The delay in the decrease of the markers of bone formation compared with those of resorption could be explained by the normal coupling between formation and resorption, since bisphosphonates did not have a direct inhibitory effect on osteoblastic bone formation. The net reduction in bone turnover led to significant increases in spinal and hip BMD ($p < 0.0001$ vs placebo) relative to baseline and a marked reduction in the incidence of vertebral fracture.

The Panel considered that although, as stated in the SPC, treatment with Bonviva led to progressive net gains in bone mass, such gains were not as a direct result of 'Building bones'. Increased bone mass was a result of a decrease in bone turnover with bone resorption being suppressed and then as a consequence of that, but not due to direct action of Bonviva, bone formation being suppressed to a lesser degree. In the Panel's view 'Building bones' implied that Bonviva had a positive effect on bone formation and that in some way it might stimulate osteoblasts which was not so. Any increase in bone mass, as a result of Bonviva therapy, was as a consequence of its main pharmacodynamic action, ie inhibition of bone resorption.

The Panel considered that 'Building bones' was a misleading claim which could not be substantiated; it implied that Bonviva had a direct bone-forming action which was not so. Breaches of Clauses 7.2 and 7.4 were ruled. This ruling was appealed.

Although noting its ruling above, the Panel did not consider that the claim was inconsistent with the Bonviva SPC which stated that therapy led to progressive net gains in bone mass. No breach of Clause 3.2 was ruled.

APPEAL BY ROCHE AND GLAXOSMITHKLINE

Roche appealed the Panel's rulings of breaches of Clauses 7.2 and 7.4 on behalf of itself and GlaxoSmithKline.

Roche explained that bone was in a constant state of flux, a process known as bone remodelling. Bone remodelling was a sum of its two parts, bone resorption and bone formation and these must be considered together in order to understand what was happening to bone ie was bone being broken down, being built or in equilibrium?

In young healthy adults there was a continuous breakdown of bone (removal of bone mass or bone mineral) and at the same time a continuous deposition (formation) of bone mineral or bone mass. If resorption and formation were to be considered in isolation one of two conclusions could possibly be drawn; (i) that bone was being broken down or (ii) bone was being built. After considering the two parts together - essential in order to understand what was happening - it was clear that the net result was neither bone breakdown nor formation but equilibrium. Bone mass was neither increasing nor decreasing.

Roche explained that in postmenopausal osteoporosis the bone remodelling process was out of balance with bone resorption being greater than bone formation. The company noted, however, that in the majority of patients it was not just bone resorption that increased after the menopause; both bone resorption and bone formation increased but with bone resorption increasing to a greater extent than bone formation. The net result was bone breakdown resulting in loss of bone mineral or bone mass. This led to a weakening of the bones that were then susceptible to fracture. It was essential to appreciate that the loss of bone in postmenopausal women was as a result of (or the sum of) combined rates of bone resorption and bone formation.

Roche submitted that the principal mechanism of action of bisphosphonates (including Bonviva) was to reduce bone resorption to premenopausal levels. Indeed bisphosphonates were widely known as, and referred to as, antiresorptives or antiresorptive agents. This reduction in bone resorption rebalanced the bone remodelling process where bone formation occurred at a greater rate than bone resorption thus allowing bone mass or bone mineral to be deposited in bone. Whilst bone formation was also reduced it was reduced by a smaller degree than bone resorption. The overall (or net) result was a deposition of bone mineral or bone mass which resulted in bone being built.

It was inaccurate to consider bone resorption and bone formation in isolation as this would not provide the correct information in relation to bone remodelling ie the overall or net effect. As acknowledged by the Panel, the net effect of treatment with Bonviva was that bone mineral or bone mass was increased. Therefore the net result was that bone was being built.

Roche noted that Servier quoted Rodan *et al* to describe the mechanism of action of bisphosphonates. As stated previously, the companies agreed with these quotations about the mechanism of action of bisphosphonates, specifically that bisphosphonates acted principally to reduce bone resorption. There was also a decrease, albeit a smaller decrease, in bone formation. However, Rodan *et al* referred to the net result of bisphosphonates in the bone remodelling process. For example, when discussing the mechanism of action of bisphosphonates at the tissue level Rodan *et al* stated 'Furthermore, the amount of new bone formed at each individual basic multicellular unit (BMU), measured by the thickness of newly formed bone, is not decreased but if anything, even increased'. Rodan *et al* continued and stated 'Bisphosphonates produce a positive calcium balance in animals and increase the amount of bone in animals and in humans'.

Roche submitted that it was clear that Servier considered that Bonviva worked merely by preventing further deterioration of osteoporotic bone and by stopping bone resorption. However, both of these statements were incorrect as highlighted by Rodan *et al*. Bonviva did not stop bone resorption; it reduced

bone resorption to premenopausal levels. The net effect of Bonviva on bone in terms of statistically significant effects on BMD was highlighted in Section 5.1 of the SPC which stated 'Ibandronic acid leads to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women' and continued in the section describing the pharmacodynamic effects stating 'Both daily and intermittent (with prolonged dose-free intervals) long-term administration in rats, dogs and monkeys was associated with formation of new bone of normal quality and maintained or increased mechanical strength even at doses in the toxic range. In humans, the efficacy of both daily and intermittent administration with a dose-free interval of 9-10 weeks of ibandronic acid was confirmed in a clinical trial (MF4411), in which Bonviva demonstrated anti-fracture efficacy'. (MF4411 was bioequivalent to the 150mg monthly dose and had been considered to be so in the MAA).

Roche submitted that in addition to the SPC the overall or net effect of treatment with Bonviva was also clearly described in the patient information leaflet reviewed and approved by regulatory authorities which stated 'Bonviva prevents loss of bone from osteoporosis, and helps to rebuild bone'.

Roche submitted that the Oxford English Dictionary defined the word 'build' as 'construct by putting parties of material together' and 'establish, make or accumulate gradually' and defined the words 'build up' as 'increase in size or strength'. Bonviva strengthened bones as a result of a gradual accumulation of bone mineral and bone mass. This fitted correctly with the Oxford English Dictionary definition 'build'. However achieved mechanistically, the fact remained that patients benefited from an increase in bone mass which led to a reduced risk of fracture. This increase in bone mass was, for the patient, building bone.

Medicines in other therapy areas also described the net result of the treatment without specifically referred to the mechanism of action. For example, angiotensin coverting enzyme inhibitors would reduce blood pressure but promotional claims did not specifically refer to the mechanism of action. A similar example might be with a diabetic treatment. The net result of a glitazone was to reduce blood glucose levels. The glitazone might work specifically by reducing insulin resistance but again it was acceptable to claim an effective reduction in blood glucose as this was what would benefit the patient, without referring to the mechanism of action ie the net result of the treatment was described without providing details of exactly how the net result was achieved.

Roche submitted that for all the reasons detailed above it considered that the overall or net effect of Bonviva treatment was that bone would be built and therefore Bonviva did build bone and so the claim 'Building bones' was not misleading and was capable of substantiation and therefore not in breach of Clauses 7.2 and 7.4.

COMMENTS FROM SERVIER

Servier alleged that the claim 'Building bones', in the context of promotion of a medicine licenced to treat osteoporosis, implied the medicine had a positive action on bone formation, a bone-forming effect. The impression given to a doctor reading this claim would be of a medicine that positively encouraged growth of bone with an anabolic effect, such as teriparatide, and not one that prevented resorption of osteoporotic bone.

Servier submitted that Bonviva actually had a negative impact on bone forming cells and could not therefore be considered to be 'Building bones'.

Servier noted that the Bonviva SPC stated that it was a 'bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation'. Indeed, osteoclasts were involved in bone resorption and were inhibited by bisphosphonates as reflected by a reduction in markers of bone resorption; whereas osteoblasts were involved in bone formation and biochemical markers of osteoblastic activity (bone-forming) were also reduced with bisphosphonates.

Servier noted that Rodan *et al*, with reference to the mechanism of action of bisphosphonates, had stated 'there is a reduction in bone turnover', 'evidenced by a decrease in both bone resorption and bone formation'. Furthermore, the authors stated that 'besides resorption, formation is decreased too, as evidenced by a reduction in the bone formation surface'. This effect on bone turnover was determined by measuring biochemical markers of bone formation and bone resorption.

Servier alleged that bisphosphonates, including Bonviva, therefore reduced bone formation and bone resorption as measured by biochemical markers. As Roche had noted, because bone formation was reduced by a smaller degree than bone resorption, the net effect was an increase in bone mass. However, the fact that bisphosphonates had a net effect on increasing bone mass did not justify the claim 'Building bones'. In contrast, a true bone building agent had an anabolic effect as reflected in increases in biochemical markers of bone formation.

Servier stated that a treatment that increased bone mass did not necessarily 'Build bones'. Indeed, bone mass could be increased by other mechanisms. With reference to bisphosphonates, Rodan *et al* stated that 'after the decrease in bone turnover…bone will have more time to complete mineralization … thus "older" bone had a higher mineral content'. This implied therefore that the bone was not new as might be expected from a medicine that built bones.

Servier noted that Roche referred to dictionary definitions of the term 'builds' and 'build up'. However the context of these definitions in terms of medicines was not appropriate especially where the term could easily be confused by the reader to mean an effect such as anabolism. Therefore, as Bonviva did not

have any anabolic action these terms were inappropriate.

Roche and GlaxoSmithKline pointed out that medicines in other therapy areas made promotional claims that described the net result of treatment without specifically referring to the mechanism of action. However, this argument did not apply to here as the claim 'Building bones', in the context of the promotion of a medicine licensed to treat osteoporosis, implied the medicine had a positive bone-forming, or anabolic effect. Following the logic that Roche set out with regard to promotional claims in other therapy areas, the claim 'Bonviva increases bone mass' would be appropriate as it referred to the net effect of Bonviva without specifically referring to its mechanism of action.

In conclusion, Servier stated that bisphosphonates, including Bonviva, increased bone mass by acting as anti-resorptive agents but did not have a positive action on bone formation, such as that expected of an anabolic agent, and therefore could not be claimed to have a 'bone building' effect. Consequently, the claim 'Building bones' was misleading and not capable of substantiation, and therefore was in breach of Clauses 7.2 and 7.4.

APPEAL BOARD RULING

The Appeal Board noted from its SPC that Bonviva acted selectively on bone tissue and specifically inhibited osteoclast formation (ie bone resorption) without directly affecting bone formation. Bonviva led to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.

The Appeal Board noted that the SPC did not refer to 'Building bones' although it did state that treatment with Bonviva led to progressive net gains in bone mass. The patient information leaflet stated that 'Bonviva prevents loss of bone from osteoporosis, and helps to rebuild bone'. The Appeal Board considered that 'leads to progressive net gains in bone mass' and helping to rebuild bone described an indirect effect of therapy whereas 'Building bones' implied that Bonviva had a positive direct effect on new bone formation and that in some way it might stimulate osteoblasts which was not so. Any increase in bone mass, as a result of Bonviva therapy, was as a consequence of its main pharmacodynamic action, ie inhibition of bone resorption.

The Appeal Board noted the respondents' submissions regarding the net clinical effect of Bonviva but nonetheless considered, on balance, that 'Building bones' was a misleading claim which could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4. The appeal was unsuccessful.

Complaint received	**12 March 2007**
Case completed	**14 June 2007**

CASE AUTH/1977/3/07

PFIZER v ASTRAZENECA

Statin documents

Pfizer complained about two items on statins which had been supported by AstraZeneca. One was a loose insert in The Pharmaceutical Journal (PJ) of 20 January entitled 'The new NICE guidance on the use of statins in practice – Considerations for implementation' which stated on the front cover that it was 'Supported by AstraZeneca'. The other was a document entitled 'Prescribing Statins – guidelines as presented by [a named] Primary Care Trust [PCT]' which stated on the front cover 'This leaflet was produced and printed using a grant from AstraZeneca'. AstraZeneca supplied Crestor (rosuvastatin) and Pfizer supplied Lipitor (atorvastatin).

The insert at issue had been the subject of Cases AUTH/1951/2/07 to AUTH/1955/2/07. When the Panel considered Case AUTH/1977/3/07, these cases were to be appealed.

Pfizer alleged that the document published with the PJ might mistakenly be taken to represent the views of NICE (the National Institute for Health and Clinical Excellence). From its appearance readers would assume that this was official NICE guidance and that NICE had stated that Crestor was a cost effective alternative after simvastatin, which was not so. Pfizer alleged that this was misleading and was disguised promotion.

The document contained Crestor material relating to cost efficacy and the Crestor cost model as data on file and a quotation about the safety of Crestor in relation to other statins. Pfizer considered that the selective use of such quotations, as well as the comparison of only Lipitor and Crestor on a cost basis prevented a balanced decision being made.

The document reproduced AstraZeneca promotional graphs and figures. Pfizer alleged that health professionals were likely to be misled as to the nature of the information and the involvement of AstraZeneca; the item was more than 'Supported by AstraZeneca' as claimed on the front page and this lack of clarity was in breach of the Code.

Pfizer considered that the supplement should have contained prescribing information, the statement on adverse event reporting, the AstraZeneca logo and the Crestor brand name.

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

The supplement in question had been sponsored/financially supported by AstraZeneca; it had been initiated by the company and its communications agency had contacted the two authors. AstraZeneca was aware of the outline of the supplement and had, at the request of one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The supplement was reviewed by AstraZeneca to ensure that it was factually correct. The two authors had full editorial control although the choice of some of the material they used was limited to that provided by AstraZeneca.

The Panel considered that AstraZeneca was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Given the company's involvement and content, the Panel considered that the supplement was, in effect, promotional material for Crestor. The Panel considered that it was disguised promotion in that the supplement appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca. The statement on the front cover 'Supported by AstraZeneca' added to the impression of independence. A breach of the Code was ruled.

The Panel did not consider that the document looked like official NICE guidance as alleged. It was clear from the title on the front cover that the supplement discussed the implementation of the guidance. The Panel considered that the supplement was not misleading and disguised in that regard and no breach of the Code was ruled.

The Panel considered that although 'Supported by AstraZeneca' did not give details about the company's role, AstraZeneca's support was clearly stated on the front cover of the supplement. No breach of the Code was ruled.

The Panel noted that given its ruling above that the supplement was, in effect, promotional material for Crestor, it should have included the prescribing information for Crestor which it did not. A breach of

the Code was ruled. The Panel noted that Pfizer had referred to the absence of a statement relating to adverse event reporting but had not cited the relevant clause in its complaint, thus no ruling could be made.

Pfizer had alleged a breach of the requirement that the non-proprietary name of a medicine appear immediately adjacent to the most prominent display of the brand name. The supplement only ever referred to rosuvastatin. There thus could be no breach of the Code and the Panel ruled accordingly.

The NICE guidance on statins recommended that when patients were first treated with a statin they should receive one with a low acquisition cost. Based on this guidance generic simvastatin would be the first choice. If patients failed to reach agreed targets on generic simvastatin they could then be switched to a more expensive statin. The Panel noted, however, that the cost data presented in the supplement, even under the heading 'Calculating the cost of implementing NICE guidance across a primary care trust population', only compared the cost of atorvastatin and rosuvastatin. There was no mention of the cost of generic simvastatin; without this data the Panel considered that it was impossible for readers to fully understand the cost implications of using a second-line statin. The data was misleading and breaches of the Code were ruled.

A cost-effectiveness model was presented in the supplement which featured two tables of data detailing the financial implications of using atorvastatin or rosuvastatin as second-line therapy to simvastatin. Both tables referred to rosuvastatin 40mg ie the maximum daily dose. According to the Crestor summary of product characteristics (SPC), in the light of increased reporting rate of adverse reactions with the 40mg dose compared to lower doses a final titration to the maximum dose of 40mg should only be considered in patients with severe hypercholesterolemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia) who did not achieve their treatment goal on 20mg and in whom routine follow-up would be performed. Specialist supervision was recommended when the 40mg dose was initiated. The SPC stated that an assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40mg. Crestor appeared to be different as specialist supervision was not required with the maximum daily dose of any of the other statins. This important condition on the use of rosuvastatin was not referred to anywhere in the supplement. The section on optimizing statin treatment strategies dismissed the possibility that rosuvastatin might be related to a higher incidence of side effects than other statins; it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The supplement was misleading with regard to the safety profile of Crestor and its comparison with other statins and breaches of the Code were ruled.

In relation to the PCT guidelines, Pfizer noted that the statin algorithm recommended using simvastatin first line up to 80mg followed by the most cost effective choice, aiming for treatment targets of total cholesterol <4mmol/L and LDL-C <2mmol/L in secondary prevention and high risk primary prevention. The efficacy and cost efficacy data presented should therefore reflect this algorithm.

However, the cost efficacy argument presented did not reflect the algorithm. The cost per 1% LDL-C reduction table highlighted rosuvastatin 5mg or 10mg as being 'the most cost effective choice after simvastatin'. However, the algorithm recommended titrating simvastatin to 80mg/day before switching therapy. The bar chart on page two showed that patients not treated to target on simvastatin 80mg would require rosuvastatin doses >20mg to obtain further efficacy. The cost efficacy of the 5mg and 10mg doses was therefore not relevant if doses with greater efficacy were required according to the algorithm.

Secondly, the PCT guidelines recommended targets of total cholesterol <4mmol/L and LDL-C <2mmol/L for secondary prevention and high risk primary prevention. A cost efficacy argument needed to consider how many patients could achieve these targets by using rosuvastatin rather than atorvastatin after simvastatin 80mg. Again, the cost per 1% LDL-C reduction as a measure of cost efficacy was not relevant in this clinical scenario where doses of rosuvastatin higher than 5mg or 10mg might be required to achieve these lower targets in patients where simvastatin 80mg had failed.

The LDL-C efficacy data presented were taken from the STELLAR trial. This trial did not include rosuvastatin 5mg but the 5mg dose was discussed in the cost-efficacy section. Pfizer noted that for several patient groups the recommended start dose was 5mg, even when switching from other statins.

On the final page the chart highlighted simvastatin 40mg, rosuvastatin 10mg and atorvastatin 40mg/80mg and encouraged the reader to compare costs. However, these doses had different efficacy and again this did not relate to the algorithm. The 5mg dose of rosuvastatin was missing as was pravastatin 40mg.

Pfizer noted the supplementary information to the Code that economic evaluation must be consistent with the product's marketing authorization. Pfizer considered that failure to discuss the dosing limitations of rosuvastatin that would be likely to be relevant following the treatment failure of simvastatin 80mg, conflicted with this aspect of the Code.

No safety data relating to any of the medicines discussed were presented. As well as preventing the formation of a balanced opinion, Pfizer alleged this was in breach of the Code, which required an unbiased and balanced view of the risk/benefit ratio of any treatment.

The data presented, the references quoted and the cost effectiveness model used focussed on AstraZeneca material, and indeed many of the graphs were taken directly from Crestor promotional material. The front of the document should therefore clearly have stated that this item was not just supported by a grant from AstraZeneca, but was written in collaboration with it and the absence of such a statement breached the Code.

Pfizer understood the document had been used by AstraZeneca's representatives in meetings with health professionals and as such prescribing information for rosuvastatin was needed.

In relation to the quotation 'Changing the million patients who currently take atorvastatin 10mg or 20mg to simvastatin 40mg should have no effect on health but would save £1.1 billion over five years' (Moon and Bogle 2006), Pfizer noted that many of the assumptions made in the cost-model used by Moon and Bogle were still debated. As such, Pfizer alleged that the quotation was unbalanced and misleading, and that it disparaged atorvastatin.

Finally, the document appeared to be PCT guidance representing that PCT's opinion. However, it was clear that AstraZeneca had had considerable involvement in its preparation. This could mislead a health professional as to the nature and source of the document and represented disguised promotion.

The Panel noted that the document had been produced and printed using a grant from AstraZeneca; it had been co-developed by AstraZeneca and the PCT. It was used by representatives, within a Crestor promotional call, as an aid to discussing the PCT's statin guidelines. AstraZeneca had thus used the document in a promotional context. The Panel also noted AstraZeneca's submission that the item was used incorrectly during a promotional call. The Panel noted that as the document referred to rosuvastatin, and made several claims for the product, the balance of probabilities was that representatives, in a Crestor promotional call, would have used the document for a promotional purpose. Given the company's creation of the document and subsequent use of it, the Panel considered that it was, in effect, promotional material for Crestor that had been disguised; the document appeared to be the independent PCT guidelines produced and printed using a grant from AstraZeneca. In that regard the Panel noted that the PCT logo was more prominent than the statement relating to AstraZeneca's support. A breach of the Code was ruled.

The Panel considered that the phrase 'This leaflet was produced and printed using a grant from AstraZeneca' gave misleading details about the company's role. A breach was ruled as acknowledged by AstraZeneca.

As the document did not include prescribing information for Crestor, a breach was ruled as acknowledged by AstraZeneca.

AstraZeneca did not answer Pfizer's allegations regarding the content of the document, although it disagreed that any content was factually incorrect or that it disparaged atorvastatin. The Panel noted that the document had been approved by AstraZeneca's signatories.

The Panel had no information about the algorithm other than that given in the document. Page 1 referred to secondary prevention target/high risk primary prevention giving targets of less than 4 for total cholesterol and LDL-C less than 2 or total cholesterol reduction of 25% and LDL-C reduction of 30% - whichever was greater. The primary prevention targets were total cholesterol less than 5 and LDL-C less than 2.5. The data on pages 2 and 3 of the document referred only to percentage reduction in LDL-C. Thus the efficacy and cost data did not reflect the algorithm. The Panel ruled that the document was misleading in this regard in breach of the Code.

A bar chart compared the percentage reduction in LDL-C from baseline for simvastatin (10-80mg), rosuvastatin (10-40mg) and atorvastatin (10-80mg). It appeared that if a greater percentage reduction was required than was possible with simvastatin 80mg (approximately -45%) then patients would have to receive either rosuvastatin (20 or 40mg) or atorvastatin (40 or 80mg). This was followed by the Moon and Bogle quotation then the claim 'Rosuvastatin, at a start dose of 5 or 10mg, is the most cost effective choice after simvastatin'. Given the content of the bar chart and the positioning of the claim the Panel considered that the claim was misleading as the cost efficacy of the 5mg and 10mg doses was irrelevant given that usually higher doses would be needed. In addition the bar chart did not give any indication of the LDL-C reduction from baseline for the 5mg dose. A breach of the Code was ruled.

Below the claim were two tables of data showing the cost per 1% LDL-C reduction for rosuvastatin (5-40mg) and atorvastatin (10-80mg). It was stated that the cost was based on pack sizes of 28 tablets. Given that the cost of 28 x 40mg rosuvastatin was £29.69 and it lowered LDL-C from baseline by 55% the cost per percentage LDL-C reduction was stated as 53 pence. This cost, however, took no account of the fact that the SPC recommended specialist supervision when the 40mg dose was initiated. Further 40mg should only be used in high risk patients in whom routine follow-up would be performed. Such follow-up would add to the cost of therapy. In that regard the Panel ruled that the data were misleading in breach of the Code.

The bar chart which compared the percentage reduction in LDL-C from baseline showed results for rosuvastatin 10mg, 20mg and 40mg. It thus appeared that the lowest dose of rosuvastatin was 10mg which was not so. A 5mg dose was available which, according to the Crestor SPC, was recommended in some patients. Although a footnote to the bar chart stated 'For recommended start and maximum doses

for individual patients, please refer to SmPC', this did not negate the otherwise misleading impression with regard to the availability of doses. A breach of the Code was ruled.

A cost comparison chart was on a page headed 'Prescribing statins' with a subheading 'Lipid Lowering Drugs – cost comparison'. The chart gave the cost for 28 days' treatment of a number of lipid lowering agents and highlighted three - simvastatin 40mg (£3.89), rosuvastatin 10mg (£18.03) and atorvastatin 40mg, 80mg (£28.21). The Panel noted that, according to the bar chart on the previous page which showed the percentage reduction in LDL-C from baseline, simvastatin 40mg would lower LDL-C by up to approximately -38%, rosuvastatin by up to -45% and atorvastatin 80mg by up to -50%. In terms of LDL-C lowing efficacy these three agents were thus not equivalent. The Panel considered, however, by highlighting these three medicines/doses, readers would assume that they were therapeutically equivalent which was not so. The footnote 'Doses given do not imply therapeutic equivalence' did not negate the impression given. A breach of the Code was ruled.

The cost comparison chart was not limited to statins; it was unclear as to the basis on which products had been chosen. Rosuvastatin had been included at doses of 10mg, 20mg and 40mg but not at 5mg. Pravastatin was included but only at a dose of 20mg although the recommended dose range was 10-40mg. The basis of the cost comparison was unclear and was thus misleading in breach of the Code.

The quotation 'Changing the million patients who currently take atorvastatin 10mg or 20mg to simvastatin 40mg should have no effect no health but would save £1.1bn over five years…' was referenced to Moon and Bogle. Pfizer had submitted that there had been some debate about the authors' assumptions but it had not provided any detail. There was no response from AstraZeneca. Nonetheless the Panel considered that not everyone who currently took 20mg atorvastatin would be suitable to change to simvastatin 40mg. In that regard the Panel noted that the percentage reduction in LDL-C from baseline for the two products was shown as approximately -41% and -38% respectively. Thus some patients on atorvastatin 20mg might fail to reach lipid targets if they were switched to simvastatin 40mg. On the information provided the Panel considered that although the short quotation from Moon and Bogle might be misleading it did not disparage atorvastatin as alleged; no breach was ruled.

The Panel ruled a breach as the document failed to present a balanced view of the risk/benefit ratio of any treatment as alleged.

Pfizer also alleged that the degree of potential confusion over the true content of the two items, the similarity of the breaches and the short time-period over which they were produced suggested consistent shortfalls within AstraZeneca.

The Panel noted that AstraZeneca had failed to recognise that the document placed in the PJ was, in effect, promotional material for Crestor. Similarly the PCT guidelines had been entered into the company's copy approval system in such a way that the intent of the originator had either not been apparent or had been misinterpreted by the signatories. The Panel considered that such flaws in the copy approval system, highlighted by the generation of both documents, were unacceptable. High standards had not been maintained. A breach of the Code was ruled.

The Panel was further very concerned that although the 40mg dose of rosuvastatin had been referred to in both documents, neither referred to the requirements in the SPC with regard to the specialist supervision and routine patient follow-up. The Panel considered that the omission of such information might prejudice patient care. The two documents had brought discredit upon and reduced confidence in the pharmaceutical industry and a breach of Clause 2 was ruled.

The Panel noted its rulings above and decided, in accordance with Paragraph 7.1 of the Constitution and Procedure, that if there was subsequently an appeal by AstraZeneca relating to the PCT guideline it would require AstraZeneca to suspend the use of the document pending the final outcome. The supplement from the PJ was already the subject of a forthcoming appeal.

The Panel considered that this case highlighted an apparent lack of control in AstraZeneca's copy approval system. Furthermore the Panel was extremely concerned that when it had asked the company for further information about the PCT guidelines AstraZeneca had submitted that it had now had the opportunity to undertake a full investigation into this complaint. This had provided greater clarity and additional information that the company was not aware of when it responded to Pfizer in February 2007. AstraZeneca's second response to the Authority differed markedly from the first. This was unacceptable. Self-regulation depended upon companies investigating matters fully at the outset and submitting full and frank responses both in inter-company correspondence and to the Authority. The Panel also noted AstraZeneca's dismissal of questions relating to the content of the PCT guidelines document.

Overall, the Panel was extremely concerned about AstraZeneca's procedures with regard to the Code including its incorrect initial responses and decided to report the company to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure.

The Appeal Board noted that AstraZeneca had accepted all of the rulings regarding the piece which had been distributed with the PJ; rather than being a sponsored supplement, as described by AstraZeneca, the Appeal Board had decided in Cases AUTH/1951/2/07 to AUTH/1955/2/07 that the piece was a paid for promotional insert for Crestor. The

Appeal Board noted that it would consider the report on the basis of the information before it in the present case (Case AUTH/1977/3/07).

The Appeal Board noted that AstraZeneca's erroneous belief that the PCT guidelines was a PCT-generated document was solely based upon a verbal communication from the relevant medical signatory. The Appeal Board was concerned that there had been no follow up investigation or documentation sought which would have shown the communication was untrue. The Appeal Board also noted AstraZeneca's submission that there was inadequate communication between the field and head office about the document. The Appeal Board was concerned that AstraZeneca had responded to both Pfizer in its inter-company correspondence and then to the Authority in its initial response to the complaint without adequate investigation. This was totally unacceptable. There was no documentation in the job bag to support PCT involvement with the generation of the guidelines. It appeared that only upon investigation of a request for further information by the Panel did AstraZeneca discover that its initial response was incorrect and so informed the Authority.

AstraZeneca had stated that the PCT guidelines had been withdrawn on 1 March. However, the Appeal Board noted that an email timed at 16:36 on 1 March highlighted the requirements of the Code relevant to the delivery of the item but allowed continued use. The Appeal Board noted from AstraZeneca that despite this permitted use, due to continuing confusion about the item's use, it had not been used beyond 1 March. The Appeal Board was concerned that the process for withdrawal of the item was uncertain. An email permitting use could not amount to effective withdrawal of use.

The Appeal Board noted that AstraZeneca accepted that errors had been made for which it apologised and provided details of corrective action taken.

The Appeal Board considered that effective and robust self-regulation relied upon companies making fully informed responses to complaints. AstraZeneca had not made sufficient investigations and as a result it had provided incorrect responses which was totally unacceptable. The Appeal Board considered this matter to be of the utmost seriousness.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of AstraZeneca's procedures in relation to the Code to be carried out by the Authority. In addition the Appeal Board decided, on the basis that it had not fully investigated the matter of the PCT guidelines when it responded to Pfizer and in its first response to the Authority, that AstraZeneca should be publicly reprimanded.

Upon receipt of the audit report, the Appeal Board considered that AstraZeneca should provide the Authority with a copy of its new standard operating procedures (SOPs). On the basis that the SOPs were provided and that the recommendations from the audit report were implemented the Appeal Board decided that no further action was required.

Pfizer Limited complained about two items on statins which had been supported by AstraZeneca UK Limited. One was a supplement to The Pharmaceutical Journal of 20 January entitled 'The new NICE guidance on the use of statins in practice – Considerations for implementation' which stated on the front cover that it was 'Supported by AstraZeneca'. The other was a document (ref CRES10213) entitled 'Prescribing Statins – guidelines as presented by [a named] Primary Care Trust [PCT]' which stated on the front cover 'This leaflet was produced and printed using a grant from AstraZeneca'.

AstraZeneca supplied Crestor (rosuvastatin) and Pfizer supplied Lipitor (atorvastatin).

1 Insert on statins in The Pharmaceutical Journal

The material had been the subject of Cases AUTH/1951/2/07 to AUTH/1955/2/07. When the Panel considered Case AUTH/1977/3/07, these cases were to be appealed.

COMPLAINT

Pfizer stated that the insert put forward opinions which might mistakenly be taken to represent the views of NICE (the National Institute for Health and Clinical Excellence), considering their presence in a review of NICE guidance. From its appearance the reader might assume that this was official NICE guidance and that NICE had stated that Crestor was a cost effective alternative after simvastatin, which was not so. Pfizer alleged that this was misleading and was disguised promotion in breach of Clause 10.1 of the Code.

Inside there was one page on NICE guidance on statins and the majority of the rest of the document contained Crestor material relating to cost efficacy and the Crestor cost model as data on file. The safety section included a quotation about the safety of Crestor in relation to other statins. Pfizer considered that the selective use of such quotations, as well as the comparison of only Lipitor and Crestor on a cost basis prevented a balanced decision being made on the basis of this material. Pfizer alleged breaches of Clauses 7.2 and 7.3.

The item reproduced AstraZeneca promotional graphs and figures. Pfizer alleged that the presentation of the piece was likely to mislead health professionals as to the nature of the information contained within and the involvement of AstraZeneca in its preparation in breach of Clause 10.1.

As a result of the inclusion of material lifted from Crestor promotional material and the use of cost models prepared by AstraZeneca, Pfizer considered this piece was certainly more than 'Supported by AstraZeneca' as claimed on the front page and alleged

that this lack of clarity concerning the company's involvement was in breach of Clause 9.10.

Given the above, Pfizer considered that the supplement was a promotional item and thus should have contained prescribing information, the usual statement on adverse event reporting, the AstraZeneca logo and the Crestor brand name. All of these were missing, in breach of Clauses 4.2 and 4.3.

The perception that this whole document could be misinterpreted as a commentary on official NICE guidance and that all the Crestor promotional material was part of the NICE guidance Pfizer considered was very serious. Indeed, Pfizer questioned whether this could be described as a NICE-related summary at all, as the majority of the text and tables related to promotion of Crestor's cost-benefit ratio, with only a limited discussion of the findings of the NICE statin guidance.

RESPONSE

AstraZeneca submitted that the supplement in question was distributed with The Pharmaceutical Journal on 20 January and written by a GP and a pharmacist and was financially supported by AstraZeneca; a sponsorship statement 'Supported by AstraZeneca' appeared on the front cover.

The supplement was developed in 2006. AstraZeneca was told that the supplement was going to be published in January 2007, however the company only became aware that it had been distributed when it was raised in discussion between a pharmacist and a member of its medical team. Subsequently, five letters of complaint appeared in The Pharmaceutical Journal and these were the subjects of Cases AUTH/1951/2/07 to AUTH/1955/2/07.

The editorial board of The Pharmaceutical Journal responded in a leading article entitled, 'We call this free speech' which clearly presented its views on the nature and purpose of the supplement. In addition, the authors had published their responses to the readers' comments. The journal had not invited AstraZeneca to comment.

During its regular discussions with health professionals AstraZeneca became aware that they were unclear as to how the recommendations published in the NICE Statin Technology Appraisal in early 2006 should be implemented, taking into consideration seemingly conflicting advice from different sets of guidelines.

The initiation of the supplement arose out of awareness of this issue. AstraZeneca's agency asked if The Pharmaceutical Journal would be interested in such an educational discussion article and when the journal confirmed that it was, the agency contacted two of the health professionals who had previously identified the issue and were interested to co-develop an outline for the article. AstraZeneca was aware of the outline and the health professionals' input to this. These health professionals were well-respected, independent medical authors who frequently contributed articles to the medical press. The two authors wrote the article themselves and had full editorial control. The GP requested the cost-effectiveness tables and information from AstraZeneca's data on file and reviewed the content. As required by the Code, AstraZeneca reviewed the document to ensure that it was factually correct and did not contravene the Code or the relevant statutory requirements. Other than this, the authors had full editorial control and the views expressed therein. Prior to publication, The Pharmaceutical Journal reviewed the supplement to ensure it met editorial standards. The supplement had not been distributed by other means.

AstraZeneca submitted that the supplement did not present itself as an official NICE document; no Department of Health (DoH) or NICE logos appeared anywhere. Furthermore, the appropriate declaration of sponsorship from AstraZeneca, as required by the Code, was on the front cover. The full title of the document, 'The new NICE guidance on the use of statins in practice - Considerations for implementation', made it clear that this was a review of issues and considerations surrounding the NICE guidance rather than any official document from NICE itself.

AstraZeneca noted that the first chapter of the review was entitled 'The NICE guidance recommendations' and, as the title implied, described NICE's recommendation. The second chapter, 'The UK cholesterol story', put the guidance into the context of other guidelines in this therapeutic area such as the National Service Framework on Coronary Heart Disease, European Atherosclerosis Society guidelines and the Joint British Societies' 2005/06 guidance. As no statin was mentioned by name in either of these two sections, it was difficult to understand how Pfizer had construed this article as intentionally implying that NICE had endorsed any of the currently available UK statins. AstraZeneca therefore denied a breach of Clause 10.1.

AstraZeneca noted that the third chapter of the supplement was entitled 'Reaching targets by optimising statin treatment strategies'. The company considered that the title clearly differentiated this section from NICE's opinions.

AstraZeneca disagreed that the supplement was intended to be or could be considered to be promotional. There was no intention to use the supplement promotionally; it was a valid educational discussion about the implementation of NICE guidance in relation to statins. The agency sought prior confirmation that this would be an interesting and valid educational topic for readers of The Pharmaceutical Journal and commissioned two writers, who were independent of AstraZeneca, to write the article. AstraZeneca sponsored the supplement, was aware of its proposed outline and reviewed it in accordance with Code requirements to check that the content was not promotional and the information was accurate and balanced.

The supplement introduced data comparing the efficacy of the four leading UK statins, based on Jones *et al* (2003). Although this was an AstraZeneca study, it was the only head-to-head comparative trial of the four most widely prescribed UK statins. Therefore its inclusion was extremely relevant in a supplement which attempted to offer health professionals guidance on choosing statin options in the management of dyslipidaemia and was consistent with the need to consider a fair representation of the balance of available evidence.

With regard to Pfizer's comments relating to safety issues, AstraZeneca noted that many health professionals continued to refer to regulatory concerns about the statin class as a result of the cerivastatin withdrawal in 2001 and the activities of Public Citizen, a US consumer group that ran a sustained multimedia campaign against Crestor following the product's launch. This had led to inappropriate negative safety perceptions about the product that the authors felt could be partly addressed in this article.

In response to this campaign and other issues around statin safety both the Food and Drug Administration (FDA) and the US National Lipid Association (NLA) had published reports confirming that all the currently available statins had similar safety profiles. The lengthier NLA report was quoted twice by the authors. Neither quotation mentioned any specific product but referred to statins having comparable safety profiles or similar. The authors chose to put the NLA report into the context of Public Citizen's campaign by mentioning the product in the introduction to these quotations.

As the only statin safety statement was one of parity across currently available [statins] and the only mention of rosuvastatin (Crestor) was relevant in this context AstraZeneca did not consider that this constituted a claim for superior safety or, in this context, any other potential breach of the Code as implied by Pfizer. AstraZeneca thus denied breaches of Clauses 7.2 and 7.3.

AstraZeneca acknowledged that figures and graphs produced by it were included in the supplement. These were provided following the authors' request for illustrations of the data referred to in the article. AstraZeneca exerted no influence on the choice of data or the graphs and figures used to illustrate the information presented. These choices were entirely those of the authors. AstraZeneca ensured that there was no visible branding on any of the items provided for the authors' consideration and ensured that the figures used looked significantly different from similar information presented in Crestor promotional materials. AstraZeneca denied a breach of Clause 10.1.

For the reasons already stated, AstraZeneca disagreed with Pfizer's view that the supplement was intended to be or could be considered to be a promotional item. There was no intention to use the supplement promotionally; it was a valid educational discussion about the implementation of NICE guidance in relation to statins. The two authors were independent of AstraZeneca. AstraZeneca sponsored the supplement, knew of the proposed outline and reviewed the supplement in accordance with Code requirements to check that the content was accurate and balanced.

Industry support for such independently written review articles was a legitimate means of providing education and debate for health professionals. AstraZeneca believed that the supplement provided valid, unbiased and appropriate educational content and topical discussion and had been produced in accordance with both the spirit and letter of the Code. AstraZeneca aimed to maintain high standards in all aspects of its internal review process as well as wishing to support respected sources of information and education for health professionals. AstraZeneca did not accept that there had been a breach of Clause 9.10.

Prescribing information and other requirements for promotional items had not been included in the supplement as it was a review article written by two independent health professionals, not a promotional item written by AstraZeneca. The information that it contained was the opinion of the independent authors and any information relating to rosuvastatin (Crestor) was presented in a balanced, factual and accurate manner taken from peer reviewed publications or publicly available documents (with the exception of the cost-effectiveness data which was supplied by AstraZeneca on request). There were no claims within this article that promoted the prescription, supply, sale or administration of Crestor. As indicated in the editorial comment in The Pharmaceutical Journal, the journal's editors also did not consider it to be promotional in nature. AstraZeneca did not therefore accept that there had been breaches of Clauses 4.2 and 4.3.

PANEL RULING

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

The supplement in question had been sponsored/financially supported by AstraZeneca. The supplement had been initiated by the company and its communications agency had contacted the two authors. AstraZeneca was aware of the outline of the supplement and had, when asked to do so by one of the authors, provided cost-effectiveness tables for rosuvastatin vs simvastatin as well as data on file. The

supplement was reviewed by AstraZeneca to ensure that it was factually correct. The two authors had full editorial control although the choice of some of the material they used was limited to that provided by AstraZeneca.

The Panel considered that AstraZeneca was inextricably linked to the production of the supplement. There was no arm's length arrangement between the provision of the sponsorship and the generation of the supplement. Given the company's involvement and content, the Panel considered that the supplement was, in effect, promotional material for AstraZeneca's product Crestor. The Panel considered that it was disguised promotion in that the supplement appeared to be independently written which was not so, the two authors had, in effect, been chosen by AstraZeneca. The statement on the front cover 'Supported by AstraZeneca' added to the impression of independence. A breach of Clause 10.1 was ruled.

The Panel considered that although the supplement was about the NICE guidance on the use of statins for the prevention of cardiovascular events, the document did not have the appearance of official NICE guidance as alleged. It was clear from the title on the front cover that the supplement discussed the implementation of the guidance. The Panel considered that the supplement was not misleading and disguised in that regard and no breach of Clause 10.1 was ruled.

Clause 9.10 of the Code required that material relating to medicines and their uses, whether promotional in nature or not, which is sponsored by a pharmaceutical company must clearly indicate that it has been sponsored by that company. The Panel considered that although the phrase 'Supported by AstraZeneca' did not give details about the company's role, AstraZeneca's support was clearly stated on the front cover of the supplement. No breach of Clause 9.10 was ruled.

The Panel noted its ruling above that the supplement was, in effect, promotional material for Crestor. The supplement should thus have included the prescribing information for Crestor which it did not. A breach of Clause 4.1 was ruled. The Panel noted that Pfizer had referred to the statement relating to adverse event reporting. The requirement to include this statement in promotional material was contained in Clause 4.10 of the Code. As Pfizer had not cited Clause 4.10 in its complaint, the Panel could make no ruling in this regard but asked that AstraZeneca be advised of its concerns.

The Panel further noted that Pfizer had alleged a breach of Clause 4.3. Clause 4.3 required, *inter alia*, the non-proprietary name of a medicine to appear immediately adjacent to the most prominent display of the brand name. The supplement at issue did not contain any reference to Crestor – the medicine was only ever referred to as rosuvastatin. There thus could be no breach of Clause 4.3 and the Panel ruled accordingly.

The Panel noted that the NICE guidance on statins recommended that when patients were first treated with a statin they should receive one with a low acquisition cost. Based on this guidance generic simvastatin would be the first choice. If patients failed to reach agreed cholesterol targets on generic simvastatin they could then be switched to a more expensive statin. The Panel noted, however, that the cost data presented in the supplement, even under the heading 'Calculating the cost of implementing NICE guidance across a primary care trust population' only compared the cost of atorvastatin (Pfizer's product, Lipitor) and rosuvastatin (Crestor). There was no mention of the cost of generic simvastatin; without this data the Panel considered that it was impossible for readers to fully understand the cost implications of using a second-line statin. In that regard the Panel considered that the data was misleading. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that a cost-effectiveness model was presented in the supplement which featured two tables of data detailing the financial implications of using atorvastatin or rosuvastatin as second-line therapy to simvastatin. Both tables referred to rosuvastatin 40mg ie the maximum daily dose. According to the Crestor summary of product characteristics (SPC), in the light of increased reporting rate of adverse reactions with the 40mg dose compared to lower doses a final titration to the maximum dose of 40mg should only be considered in patients with severe hypercholesterolemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia) who did not achieve their treatment goal on 20mg and in whom routine follow-up would be performed. Specialist supervision was recommended when the 40mg dose was initiated. Section 4.4 of the SPC stated that an assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40mg. Crestor appeared to be different as specialist supervision was not required with the maximum daily dose of any of the other statins (atorvastatin, fluvastatin, pravastatin and simvastatin). This important condition on the use of rosuvastatin was not referred to anywhere in the supplement. In the section on optimizing statin treatment strategies the possibility that rosuvastatin might be related to a higher incidence of side effects than other statins was discussed. This possibility was dismissed and it was stated that 'all currently marketed statins have a similar very low risk of serious adverse events' and that 'rosuvastatin gives rates of adverse events similar to those of other statins'. The Panel considered that the supplement was misleading with regard to the safety profile of Crestor and its comparison with other statins. Breaches of Clauses 7.2 and 7.3 were ruled.

2 PCT Prescribing Statins guidelines document

COMPLAINT

Pfizer noted that the PCT statin algorithm recommended using simvastatin first line up to 80mg (as 2 x 40mg) followed by the most cost effective choice, aiming for treatment targets of total cholesterol <4mmol/L and LDL-C <2mmol/L in secondary

prevention and high risk primary prevention. The efficacy and cost efficacy data presented should therefore reflect this algorithm.

However, the cost efficacy argument presented did not reflect the algorithm. The cost per 1% LDL-C reduction table highlighted rosuvastatin 5mg or 10mg as being 'the most cost effective choice after simvastatin'. However, the algorithm recommended titrating simvastatin to 80mg/day before switching therapy. The bar chart on page two showed that patients not treated to target on simvastatin 80mg would require rosuvastatin doses >20mg to obtain further efficacy. The cost efficacy of the 5mg and 10mg doses was therefore not relevant if doses with greater efficacy were required according to the algorithm.

Secondly, the PCT guidelines recommended targets of total cholesterol <4mmol/L and LDL-C <2mmol/L for secondary prevention and high risk primary prevention. A cost efficacy argument needed to consider how many patients could achieve these targets by using rosuvastatin rather than atorvastatin after simvastatin 80mg. Again, the cost per 1% LDL-C reduction as a measure of cost efficacy was not relevant in this clinical scenario where doses of rosuvastatin higher than 5mg or 10mg might be required to achieve these lower targets in patients where simvastatin 80mg had failed.

The LDL-C efficacy data presented were taken from the STELLAR trial. This trial did not include rosuvastatin 5mg but the 5mg dose was discussed in the cost-efficacy section. Pfizer noted that for several patient groups (elderly >70 years, patients with moderate renal impairment, patients with risk factors for myopathy and patients of Asian origin) the recommended start dose was 5mg, even when switching from other statins.

On the final page the chart highlighted simvastatin 40mg, rosuvastatin 10mg and atorvastatin 40mg/80mg and encouraged the reader to compare the costs of these. However, these doses had different efficacy and again this did not relate to the algorithm. The 5mg dose of rosuvastatin was missing from the chart as was pravastatin 40mg.

Pfizer alleged that these shortcomings represented a breach of Clause 7.2. Pfizer noted the supplementary information to Clause 7.2 on the economic evaluation of medicines, which stated that economic evaluation must be consistent with the product's marketing authorization. Pfizer considered that failure to discuss the dosing limitations of rosuvastatin that would be likely to be relevant following the treatment failure of simvastatin 80mg, conflicted with this aspect of the Code.

It should also be noted that no safety data relating to any of the medicines discussed were presented. As well as preventing the formation of a balanced opinion based on the information in the document, Pfizer believed this was in breach of Clause 7.10, which required that promotional material clearly represented an unbiased and balanced view of the risk/benefit ratio of any treatment.

The data presented, the references quoted and the cost effectiveness model used were very focussed on AstraZeneca material, and indeed many of the graphs were taken directly from Crestor promotional material, differing only in the absence of the Crestor colour coding. The wording on the front of the leaflet should therefore have clearly stated that this item was not just supported by a grant from AstraZeneca, but was written in collaboration with it. Pfizer alleged the absence of such a statement breached Clause 9.10.

Pfizer understood the document had been used by AstraZeneca's representatives in meetings with health professionals ie it was being used as a promotional piece and as such must have prescribing information for rosuvastatin firmly attached, as stated in Clause 4.1. It was therefore in breach of Clause 4.1.

The document contained the quotation 'Changing the million patients who currently take atorvastatin 10mg or 20mg to simvastatin 40mg should have no effect on health but would save £1.1 billion over five years' (Moon and Bogle 2006). In relation to this, Pfizer noted the supplementary information to Clause 7.2 which stated 'Where a clinical or scientific issue exists which has not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue is treated in a balanced manner in promotional material'. As highlighted in a letter to the BMJ (Lloyd 2006), debate still existed concerning many of the assumptions made in the cost-model used by Moon and Bogle. As such, Pfizer alleged that a single statement taken from this editorial was unbalanced and misleading, and that it disparaged atorvastatin in breach of Clause 8.1.

Finally, viewed as a stand-alone item, the document appeared to be guidance which was written by the PCT and which represented an opinion which it itself had formed. However, considering that the focus was solely on rosuvastatin data and Crestor promotional material, it was clear that AstraZeneca had had considerable involvement in its preparation. This could mislead a health professional as to the nature and source of the material they were receiving and represented disguised promotion in breach of Clause 10.1.

RESPONSE

When asked by the Panel for further information following consideration of its initial response, AstraZeneca submitted a wholly new response to this part of Pfizer's complaint. The company submitted that it had now undertaken a full investigation into this complaint, including conversations with the relevant personnel. This had provided greater clarity and additional information that the company was not aware of when it responded to Pfizer in February 2007.

AstraZeneca explained that following a change of local policy the PCT distributed its guidelines within the 'Statin Special' Prescribing Newsletter of March 2006.

Through subsequent conversations between AstraZeneca and the PCT, AstraZeneca became aware that the PCT was willing to discuss support that AstraZeneca could provide in dissemination of the guidelines messages to local GPs. It was subsequently agreed that AstraZeneca would support the PCT by distributing the content of its lipid guidelines by creating a bespoke item.

The item was then co-developed by AstraZeneca and the PCT. The final wording and layout was approved by the PCT. Discussions between field and head office personnel at that stage, acknowledged the fact that the item would require AstraZeneca's approval. The item was then entered in the internal AstraZeneca review process and approved for use.

The signatories reviewed the item on the understanding that it was a document created by the PCT, for which AstraZeneca paid for the production and printing under Clause 18.4. However, it became apparent before the final item production that the intent was for representatives to distribute the item. In the initial investigation, AstraZeneca understood that guidance was given verbally to the relevant AstraZeneca field personnel when the item became available for use, advising how it should be used in order to ensure that it was delivered as a service to medicine within the requirements of the Code.

Following Pfizer's allegation that AstraZeneca representatives were using the item within a promotional call, the relevant managers were contacted and both verbal and written clarification was restated on how the item should be used. Pfizer was unable to provide evidence that the item had been used to promote Crestor and at that time AstraZeneca did not think that the item was being used to promote Crestor.

AstraZeneca had now investigated further. In its opinion, both the nature of AstraZeneca's involvement in the item and the intent of how the item would be used were not interpreted in the same way by the originator and the final signatories from the outset. This misunderstanding had led to subsequent confusion of implementation. Whilst the intent of the originator was for the item to be used by the sales teams to support the PCT guidelines, the level of involvement that had already taken place prior to the item being entered into the approval system was not evident to the signatories. Additionally, upon approval of the item the requirements relating to the method of final distribution were not made explicit from head office back to the field team, as the company had originally understood to be the case.

It appeared that the verbal guidance from head office to the field that should have taken place when the item was delivered to the sales team did not happen. The sales manager and the original AstraZeneca contact with the PCT, believing that they were delivering a legitimately approved item, advised the local AstraZeneca representatives (approximately three at that time) that, should the doctor raise the local guidelines in a call then this item could be used in the discussion, with the support of the PCT. The item was therefore used as a discussion aid for the PCT guidelines within a promotional call for Crestor. AstraZeneca had no evidence to believe that Crestor was promoted from this item.

In response to the concerns raised by Pfizer, since AstraZeneca believed that this item was being approved for use as a service to medicine, it was not considered appropriate for the company to comment on the data therein that represented the PCT's guidelines. The additional data that was included in the item but which did not appear in the PCT Newsletter, had informed the original guideline recommendation as indicated on the front page of this item. AstraZeneca did not input into the writing of the PCT guidelines, therefore the company did not consider it was appropriate for it to answer Pfizer's criticism of the content and the scientific rationale behind it. AstraZeneca also disagreed that there was any content that was factually incorrect or that could be construed as disparaging to atorvastatin.

AstraZeneca accepted that the sponsorship statement did not accurately reflect the funding of this item, as no grant was given to the PCT during this collaboration. AstraZeneca paid for the layout and printing of the item. Therefore it acknowledged a breach of Clause 9.10.

AstraZeneca also acknowledged that since this item was incorrectly used within a promotional call, and because AstraZeneca has some involvement in the creation of the item, as it did not include prescribing information it breached Clause 4.1. However, since the brand name 'Crestor' did not feature in the item, it refuted that there was any case to answer in relation to Clause 4.3.

AstraZeneca's investigation suggested that this was an isolated incident occurring only within the one area, due to a combination of factors, which included the fact that this type of collaboration to communicate guidelines had not occurred before and the inexperience of the individuals involved. AstraZeneca also believed strongly that the original intent to provide support, via the local sales team, to the PCT was legitimate. On receiving the Pfizer inter-company complaint, action was taken with a prompt re-briefing issued to the field teams and subsequently to relevant team members. Use of the item ceased whilst the investigation was taking place. In light of this complaint the PCT personnel had been contacted and would be informed of the content of its response. AstraZeneca had already started to develop a policy for the correct procedures for co-development of such materials in full compliance with Clause 18.4.

In conclusion AstraZeneca believed there was a clear miscommunication and a lack of clarity between its field force and head office which warranted rulings of a breach of Clauses 4.1 and 9.10. AstraZeneca was grateful that this matter was brought to its attention so that it could take the steps outlined in this letter to prevent any such future misunderstandings.

PANEL RULING

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

The document in question had been produced and printed using a grant from AstraZeneca; it had been co-developed by AstraZeneca and the PCT. The document was used by representatives, within a Crestor promotional call, as an aid to discussing the PCT's statin guidelines. AstraZeneca had thus used the document in a promotional context. The Panel also noted AstraZeneca's submission that the item was used incorrectly during a promotional call. The Panel noted that as the document referred to rosuvastatin, and made several claims for the product, the balance of probabilities was that representatives, in a Crestor promotional call, would have used the document for a promotional purpose. Given the company's creation of a bespoke document and subsequent use of it, the Panel considered that it was, in effect, promotional material for AstraZeneca's product, Crestor. The Panel considered that it was disguised promotion in that the document appeared to be the independent PCT guidelines produced and printed using a grant from AstraZeneca. In that regard the Panel noted that the PCT logo was more prominent than the statement relating to AstraZeneca's support. A breach of Clause 10.1 was ruled.

Clause 9.10 of the Code required that material relating to medicines and their uses, whether promotional in nature or not, which was sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company. The Panel considered that the phrase 'This leaflet was produced and printed using a grant from AstraZeneca' gave misleading details about the company's role. A breach of Clause 9.10 was ruled as acknowledged by AstraZeneca.

The Panel noted its ruling above that the document was, in effect, promotional material for Crestor. The supplement should thus have included the prescribing information for Crestor which it did not. A breach of Clause 4.1 was ruled as acknowledged by AstraZeneca.

The Panel noted that, in response to Pfizer's allegations regarding the content of the document, AstraZeneca had stated that it did not consider it appropriate for the company to answer such allegations. AstraZeneca, however, disagreed that there was any content that was not factually correct or that could not be construed as disparaging to atorvastatin. The Panel noted that the document had been approved by AstraZeneca's signatories.

The Panel noted that it had no information about the PCT algorithm other than that given in the document at issue. Page 1 referred to secondary prevention target/high risk primary prevention giving targets of less than 4 for total cholesterol and LDL-C less than 2 or total cholesterol reduction of 25% and LDL-C reduction of 30% - whichever was greater. The primary prevention targets were total cholesterol less than 5 and LDL-C less than 2.5. The data on pages 2 and 3 of the document referred only to percentage reduction in LDL-C. Thus the efficacy and cost data did not reflect the algorithm. The Panel ruled that the document was misleading in this regard in breach of Clause 7.2.

The Panel noted that a bar chart compared the percentage reduction in LDL-C from baseline for simvastatin (10-80mg), rosuvastatin (10-40mg) and atorvastatin (10-80mg). It appeared that if a greater percentage reduction was required than was possible with simvastatin 80mg (approximately -45%) then patients would have to receive either rosuvastatin (20 or 40mg) or atorvastatin (40 or 80mg). This was followed by the Moon and Bogle quotation then the claim 'Rosuvastatin, at a start dose of 5 or 10mg, is the most cost effective choice after simvastatin'. Given the content of the bar chart and the positioning of the claim the Panel considered that the claim was misleading as the cost efficacy of the 5mg and 10mg doses were irrelevant given that usually higher doses would be needed. In addition the bar chart did not give any indication of the LDL-C reduction from baseline for the 5mg dose. A breach of Clause 7.2 was ruled.

Below the claim were two tables of data showing the cost per 1% LDL-C reduction for rosuvastatin (5-40mg) and atorvastatin (10-80mg). It was stated that the cost was based on pack sizes of 28 tablets. Given that the cost of 28 x 40mg rosuvastatin was £29.69 and it lowered LDL-C from baseline by 55% the cost per percentage LDL-C reduction was stated as 53 pence. This cost, however, took no account of the fact that the SPC recommended specialist supervision when the 40mg dose was initiated. Further 40mg should only be used in high risk patients in whom routine follow-up would be performed. Such follow-up would add to the cost of therapy. In that regard the Panel considered that the data was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that the bar chart which compared the percentage reduction in LDL-C from baseline showed results for rosuvastatin 10mg, 20mg and 40mg. It thus appeared that the lowest dose of rosuvastatin was 10mg which was not so. A 5mg dose was available which, according to the Crestor SPC, was recommended in, *inter alia*, patients >70 years or those with moderate renal impairment. Although a footnote to the bar chart stated 'For recommended start and maximum doses for individual patients,

please refer to SmPC', this did not, in the Panel's view, negate the otherwise misleading impression with regard to the availability of doses. A breach of Clause 7.2 was ruled.

The Panel noted that a cost comparison chart was on a page headed 'Prescribing statins' with a subheading 'Lipid Lowering Drugs – cost comparison'. The chart listed a number of lipid lowering agents and gave their cost for 28 days' treatment. The least expensive option was simvastatin 20mg (£1.71) and the most expensive was colestipol 20mg at £56.19. Three agents were highlighted – simvastatin 40mg (£3.89), rosuvastatin 10mg (£18.03) and atorvastatin 40mg, 80mg (£28.21). The Panel noted that, according to the bar chart on the previous page which showed the percentage reduction in LDL-C from baseline, simvastatin 40mg would lower LDL-C by up to approximately -38%, rosuvastatin by up to -45% and atorvastatin 80mg by up to -50%. In terms of LDL-C lowing efficacy these three agents were thus not equivalent. The Panel considered, however, by highlighting these three medicines/doses, readers would assume that they were therapeutically equivalent which was not so. The footnote 'Doses given do not imply therapeutic equivalence' did not negate the impression given. The Panel considered that cost comparison chart was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that the cost comparison chart was not limited to statins; it was unclear as to the basis on which products had been chosen. Rosuvastatin had been included but only at doses of 10mg, 20mg and 40mg. The cost of rosuvastatin 5mg was not stated. Pravastatin was included but only at a dose of 20mg although the recommended dose range was 10-40mg daily. The Code stated that valid price comparisons could only be made where like was compared with like The basis of the cost comparison shown in the PCT statins guidelines was unclear and in this regard the document was misleading. A breach of Clause 7.2 was ruled.

The Panel noted that the quotation 'Changing the million patients who currently take atorvastatin 10mg or 20mg to simvastatin 40mg should have no effect no health but would save £1.1bn over five years…' was referenced to Moon and Bogle. Pfizer had submitted that there had been some debate about the assumptions made by the authors but had not provided any detail in that regard. There was no response from AstraZeneca. Nonetheless the Panel considered that not everyone who currently took 20mg atorvastatin would be suitable to change to simvastatin 40mg. In that regard the Panel noted that the percentage reduction in LDL-C from baseline for the two products was shown in the document at issue as approximately -41% and -38% respectively. Thus some patients on atorvastatin 20mg might fail to reach lipid targets if they were switched to simvastatin 40mg. On the information provided the Panel considered that the single, short quotation from Moon and Bogle might be misleading in this regard but nonetheless it did not disparage atorvastatin as alleged and so no breach of Clause 8.1 was ruled.

The Panel noted its rulings above. The Panel considered that the guideline failed to present a balanced view of the risk/benefit ratio of any treatment as alleged. A breach of Clause 7.10 was ruled.

3 Alleged breaches of Clauses 2 and 9.1

COMPLAINT

Pfizer alleged that the degree of potential confusion over the true content of the two items considered above, the similarity in nature of the breaches contained within and the short time-period over which they were produced suggested consistent shortfalls within AstraZeneca and, as such, breaches of Clauses 9.1 and 2.

RESPONSE

AstraZeneca did not consider that the circumstances set out above warranted a ruling of a breach of Clause 9.1 and of Clause 2 of the Code solely in relation to the PCT guidelines and did not consider that Pfizer was alleging this in any event. The company did not accept that there had been any breach of the Code in relation to the supplement in The Pharmaceutical Journal therefore it did not consider a ruling of the breach of Clause 2 based on multiple, cumulative breaches of a similar and serious nature in the same therapeutic area within a short period of time was justified.

In any event, the facts behind the supplement in The Pharmaceutical Journal were substantially similar to those concerning Cases AUTH/1951/2/07 to AUTH/1955/2/07. Since these cases were the subject of an appeal it would be inappropriate and premature to conclude a definitive ruling of a breach of Clause 2 for this Case AUTH/1977/3/07.

AstraZeneca's internal procedures in relation to promotional copy-review and approval were an integral part of the company's commercial activities and reflected an intention to ensure the highest ethical standards in its communications with the health professionals and other external customers. The company viewed it's obligations to the Code as an essential part of this activity.

AstraZeneca did not therefore accept that there had been breaches of Clauses 2 and 9.1.

PANEL RULING

The Panel noted that AstraZeneca had failed to recognise that the document placed in The Pharmaceutical Journal was, in effect, promotional material for Crestor. Similarly the PCT guidelines document had been entered into the company's copy approval system in such a way that the intent of the originator had either not been apparent or had been misinterpreted by the signatories. The Panel considered that such flaws in the copy approval system, highlighted by the generation of both documents, were unacceptable. High standards had

not been maintained. A breach of Clause 9.1 was ruled.

The Panel was further very concerned that although the 40mg dose of rosuvastatin had been referred to in both documents, neither referred to the requirements in the SPC with regard to the specialist supervision and routine patient follow-up needed with such a dose. The Panel considered that the omission of such information might prejudice patient care. The Panel considered that in this regard, the two documents had brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted its rulings above and in accordance with Paragraph 7.1 of the Constitution and Procedure decided that if there was subsequently an appeal by AstraZeneca relating to the PCT Prescribing Statins guideline document it would require AstraZeneca to suspend the use of the document pending the final outcome. The supplement from The Pharmaceutical Journal was already the subject of a forthcoming appeal.

The Panel considered that this case highlighted an apparent lack of control in AstraZeneca's copy approval system. Furthermore the Panel was extremely concerned that when it had asked the company for further information about the PCT guidelines document, AstraZeneca had submitted a wholly different response to the Authority from its first one. In its second response the company had submitted that it had now had the opportunity to undertake a full investigation into this complaint, including conversations with the relevant personnel. This had provided greater clarity and additional information that the company was not aware of when it responded to Pfizer in February 2007. AstraZeneca's second response to the Authority differed markedly from the first. This was unacceptable. Self-regulation depended upon companies investigating matters fully at the outset and submitting full and frank responses both in inter-company correspondence and to the Authority. The Panel also noted AstraZeneca's dismissal of questions relating to the content of the PCT guidelines document.

Overall, the Panel was extremely concerned about AstraZeneca's procedures with regard to the Code including its incorrect initial responses and decided to report the company to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure.

APPEAL BOARD CONSIDERATION

The Appeal Board noted that AstraZeneca had accepted all of the rulings regarding the piece which had been distributed with The Pharmaceutical Journal; rather than being a supplement in The Pharmaceutical Journal, as described by AstraZeneca, the Appeal Board had previously decided in Cases AUTH/1951/2/07 to AUTH/1955/2/07 that the piece was a paid for insert in the journal not a supplement sponsored by The Pharmaceutical Journal. The Appeal Board had considered that the insert was promotional material for Crestor. The Appeal Board noted that it would consider the report on the basis of the information before it in the present case (Case AUTH/1977/3/07).

The Appeal Board noted from AstraZeneca that its erroneous belief that the PCT Prescribing Statins guidelines document was a PCT-generated document was solely based upon a verbal communication from the medical signatory responsible for the piece. The Appeal Board was concerned that there had been no follow up investigation or documentation sought to confirm whether this was correct. Had this been done it would have shown the communication was untrue. The Appeal Board also noted AstraZeneca's submission that there was inadequate communication between the field and head office about the PCT document. The Appeal Board was concerned that AstraZeneca had responded to both Pfizer in its inter-company correspondence and then to the Authority in its initial response to the complaint without adequate investigation. This was totally unacceptable. There was no documentation in the job bag to support PCT involvement with the generation of the guidelines. It appeared that only upon investigation of a request for further information by the Panel did AstraZeneca discover that its initial response was incorrect and so informed the Authority.

The Appeal Board noted that AstraZeneca had stated that the PCT Prescribing Statins guidelines document had been withdrawn on 1 March. However, the Appeal Board noted that an email timed at 16:36 on 1 March highlighted the requirements of the Code relevant to the delivery of the item but allowed continued use. The Appeal Board noted from AstraZeneca that despite this permitted use, due to continuing confusion about the item's use, verbal confirmation had been ascertained from the field force forum that the item had not been used beyond 1 March. The Appeal Board was concerned that the process for withdrawal of the item was uncertain. An email permitting use could not amount to effective withdrawal of use.

The Appeal Board noted the submission from AstraZeneca which accepted that errors had been made. AstraZeneca apologised for the errors and provided details of the corrective action it had taken.

The Appeal Board considered that effective and robust self-regulation was reliant upon companies making fully informed responses to complaints. AstraZeneca had not made sufficient investigations and as a result it had provided incorrect responses which was totally unacceptable. The Appeal Board considered this matter to be of the utmost seriousness.

The Appeal Board decided in accordance with Paragraph 11.3 of the Constitution and Procedure to require an audit of AstraZeneca's procedures in relation to the Code to be carried out by the Authority. On receipt of the audit report the Appeal

Board would decide whether any further action was required. In addition the Appeal Board decided, on the basis that it had not fully investigated the matter of the PCT Prescribing Statins guidelines when it responded to Pfizer and in its first response to the Authority, that AstraZeneca should be publicly reprimanded.

Upon receipt of the audit report, the Appeal Board considered that AstraZeneca should provide the Authority with a copy of its new standard operating procedures (SOPs). On the basis that the SOPs were provided and that the recommendations from the audit report were implemented the Appeal Board decided that no further action was required.

Complaint received	**16 March 2007**
Case completed	**21 June 2007**
Report to the Appeal Board	**19 July 2007**

MEDIA/DIRECTOR and ANONYMOUS v SANOFI PASTEUR MSD

Promotion of Gardasil and arrangements for a meeting

Articles entitled 'Alarm at 'battering ram' tactics over cervical cancer' and 'Vaccination campaign funded by drug firm', published in The Guardian on 26 March, criticised the promotion of Gardasil (human papillomavirus (HPV) vaccine) and the activities of Sanofi Pasteur MSD. In accordance with established practice the criticisms were taken up by the Director as a complaint under the Code (Case AUTH/1980/3/07). In Case AUTH/1983/3/07, concerns about the same articles were raised by an anonymous complainant.

Among other criticisms in the articles in The Guardian a leading public health expert likened the tactics of drug companies to 'a battering ram at the Department of Health and carpet bombing on the peripheries'. She feared the push towards mass vaccination could damage the very successful UK screening programme. She said that the vaccine was scientifically brilliant, but should be introduced carefully, not least because today's women would need to be screened for the rest of their lives. She was quoted as saying that pharmaceutical companies had tried to recruit her among the many 'opinion leaders' invited to meetings which they would be paid £1,000 to attend.

She also commented on the number of letters from representatives offering to help her plan the introduction of the vaccine. 'They wrote to every doctor of public health, every chief executive, every pharmacy adviser, senior people in the faculty of public health, all infectious disease specialists and primary care staff,' she said. Where she was based the health protection department, cancer network and screening staff together urged a national policy on the vaccine and advised staff not to talk to representatives.

The articles criticised the first global summit against cervical cancer held in Paris on 22 March which launched a Coalition against Cervical Cancer with a charter signed by female celebrities. The Coalition would lobby for mass vaccination. Journalists and celebrities were paid to attend. UK freelance journalists had not only their travel, meals and accommodation but also time paid for by the pharmaceutical company. The Club Européan de la Santé (CES) organised the meeting on the condition that Sanofi Pasteur MSD paid for it. Concern was expressed that Sanofi-Pasteur MSD was the sole funder. This charitable organisation could not have been involved if Sanofi Pasteur MSD had not offered money. The anonymous complainant had similar criticisms which were conveyed by means of annotated copies of the articles.

The Panel noted that Sanofi Pasteur MSD had invited the public health expert to participate in an advisory board in June 2005. The invitation described the advisory board as a multidisciplinary advisory panel of NHS stakeholders to discuss clinical, service and funding issues relating to the introduction of HPV vaccines into the NHS. The agenda would run from 11am to 4pm. An honorarium of £500 would be paid and all travelling expenses reimbursed. Confidentiality agreements would be signed. The Panel queried whether the invitation made the amount of work required sufficiently clear given that invitees were not sent a copy of the agenda at this stage. The final agenda ran from 10.30am to 4pm and provided plenty of opportunity for participation and discussion. The agenda was not unreasonable given the stated purpose of the meeting. Overall the Panel considered that the honorarium of £500 to participate in the advisory board as described in the invitation was not unreasonable. The invitation made the role of participants sufficiently clear. The Panel noted the amount of work actually required. The payment was for genuine services. It was not inappropriate to offer to pay attendees of the advisory board in question. No breach of the Code was ruled.

In relation to the number of letters from representatives, the Panel noted Sanofi Pasteur MSD's submission that the expert had received no promotional mailings for Gardasil. A Sanofi Pasteur MSD healthcare development executive had tried to arrange a meeting with three people within the expert's local Primary Care Trust (PCT) responsible for policy decisions on budgets but the expert had written back, via the company's head office, explaining that a meeting was not necessary given the PCT's current position on vaccination policy. Despite this letter the Panel was concerned that some eight days later the same healthcare development executive sought an appointment with the expert, the company not having forwarded a copy of her earlier letter. The company also noted that subsequent to the grant of the marketing authorization in September 2006 Sanofi Pasteur MSD's medical director wrote to the expert about a position statement on HPV vaccine which she co-authored. The position statement had advised staff to decline invitations to see company representatives. No one company was identified. She responded stating that she was reassured by Sanofi Pasteur MSD's response.

Overall the Panel did not consider that the volume of mailings sent by Sanofi Pasteur MSD was unacceptable. No promotional mailings about Gardasil had been sent to the expert. Nor was the frequency of contact made by healthcare

development executives unacceptable. The Panel ruled no breach of the Code.

In relation to the meeting held in Paris, the first thing that the Panel had to consider was whether it, or any aspect of it, came within the scope of the Code. The meeting was sponsored by Sanofi Pasteur MSD's French headquarters. The article 'Vaccination campaign funded by drug firm' noted the President of CES, a public health institution, had agreed to participate only on condition that Sanofi Pasteur MSD paid. The response from the company stated that the meeting was organised by CES – implying that CES had more than a participatory role. The position was unclear. The Panel noted that the agenda featured both European and non European (US and South American) speakers and addressed global issues in relation to cervical cancer. Twenty five UK delegates attended (11 health professionals, 13 journalists and 1 representative from a patient group). The presentations were directed to all the delegates; no material was presented during the main agenda which solely addressed a UK audience. A breakfast meeting had been held solely for UK journalists. The Panel considered that the Code applied to the invitation and the hospitality (accommodation, travelling and subsistence) provided to UK delegates. The Panel considered that the Code also applied to all of the arrangements in relation to and content of the breakfast briefing.

The breakfast briefing, organised by Sanofi Pasteur MSD UK and attended by journalists from the UK and Ireland, enabled delegates to question a panel of UK experts in the field of cervical cancer. It was chaired by a medical adviser from the UK company. The Panel did not have a copy of the invitation to the breakfast briefing. No PowerPoint presentations were made and nor were any additional materials made available. The Panel considered that it had no evidence before it to show on the balance of probabilities that either the discussions or the arrangements were unacceptable under the Code.

The Panel noted that the arrangements for UK delegates should comply with the Code. The 2006 edition of the Code extended the requirements to apply to journalists and patient groups for the first time. The Panel noted that travel was economy or standard class rail travel. The meeting venue did not appear unreasonable. Overnight accommodation was offered. It was unclear how many UK delegates had been provided with accommodation. Overall the Panel did not consider that the accommodation, travel and subsistence provided were unacceptable in relation to the requirements of the Code.

UK journalists had been provided with a certified invitation by a UK agency. Due to human error UK health professionals and others had been invited using an uncertified version of the invitation by a French based agency. The uncertified two page invitation only referred to the company sponsorship at the end, as a postscript. The Code required sponsorship to be declared such that the reader was aware of it at the outset. A breach was ruled in relation to the invitation to UK health professionals and others.
UK freelance journalists were paid 1.5 times their daily rate to attend. The supplementary information to the Code stated that funding must not be offered to a health professional to compensate them merely for the time spent in attending meetings. Meetings organised for or attended by, *inter alia*, journalists should comply with the Code. There were differences in the role played at such meetings by journalists and health professionals. There were situations where it was legitimate to pay a health professional or journalist for their time when attending meetings such as participation on advisory boards or when they were otherwise being employed to undertake a specific piece of work so long as in each case the arrangements as a whole complied with the Code. On the evidence before the Panel it appeared that the journalists were simply delegates; they were not being paid for the benefit of their expertise or to undertake a specific piece of work. In such circumstances the payments were inappropriate. Their freelance status was irrelevant. A breach of the Code was ruled. High standards had not been maintained and a further breach was ruled.

Articles entitled 'Alarm at 'battering ram' tactics over cervical cancer' and 'Vaccination campaign funded by drug firm' published in The Guardian on 26 March criticised the promotion of Gardasil (human papillomavirus (HPV) vaccine) and the activities of Sanofi Pasteur MSD Ltd. In accordance with established practice the criticisms in these articles were taken up by the Director as a complaint under the Code (Case AUTH/1980/3/07).

In Case AUTH/1983/3/07, concerns about the same articles were raised by an anonymous complainant.

Case AUTH/1980/3/07

COMPLAINT

Among other criticisms in the articles in The Guardian a leading public health expert likened the tactics of drug companies to 'a battering ram at the Department of Health and carpet bombing on the peripheries'. She feared the push towards mass vaccination could do damage to screening programmes, such as the very successful one in Britain. She said that the vaccine was scientifically brilliant, but should be introduced carefully, not least because today's women would continue to need screening for the rest of their lives. She was quoted as saying that pharmaceutical companies had tried to recruit her among the many 'opinion leaders' invited to meetings which they would be paid £1,000 to attend. She also commented on the number of letters from sales representatives offering to help her plan the introduction of the vaccine. 'They wrote to every doctor of public health, every chief executive, every pharmacy adviser, senior people in the faculty of public health, all infectious disease specialists and primary care staff,' she said. Where she was based the health protection department, cancer network and screening staff in a joint statement urged a national policy on the vaccine and advised staff not to talk to reps, 'and to let us know if they bother you'.

The articles criticised the first global summit against cervical cancer held in Paris on 22 March which launched a Coalition against Cervical Cancer with a charter signed by female celebrities. The Coalition would lobby for mass vaccination. Journalists and celebrities were paid to attend. UK freelance journalists had not only their travel, meals and accommodation but also time paid for by the pharmaceutical company. The Club Européan de la Santé (CES) organised the meeting on the condition that Sanofi Pasteur MSD paid for it. Concern was expressed that Sanofi-Pasteur MSD was the sole funder.

This charitable organisation could not have been involved if Sanofi Pasteur MSD had not offered money.

Case AUTH/1983/3/07

COMPLAINT

The anonymous complainant had similar criticisms which were conveyed by means of annotated copies of the articles.

Cases AUTH/1980/3/07 and AUTH/1983/3/07

When writing to Sanofi Pasteur MSD about the two cases, the Authority asked it to respond in relation to Clauses 7.2, 12.2, 18.1, 19.1, 19.3 and 20.3 of the Code and, in addition, Clauses 2 and 9.1 in relation to each matter and cumulatively.

RESPONSE

Sanofi Pasteur MSD noted that the two articles contained a number of inaccuracies and misleading statements, not least the headline on the front page. In brief, these were as follows.

1 The Coalition against Cervical Cancer was not a 'vaccination campaign' but rather a concerted effort, supported by many respected organisations, to eradicate cervical cancer worldwide through the combination of improved education, screening, treatment and implementation of vaccination. Sanofi Pasteur MSD would demonstrate that the meeting in Paris addressed this in a holistic and balanced way.
2 The Paris meeting did not cost one million, l*et al*one 'millions', irrespective of whether the unwritten unit was pounds or euros.
3 HPV vaccines were not 'only effective in young girls'. The only licensed HPV vaccine, Gardasil, was indicated for the prevention of cervical cancer in females aged 9 to 26 years (summary of product characteristics (SPC)). GlaxoSmithKline was seeking a licence for its vaccine in females aged 10 to 55 years.
4 Club Européan de la Santé (CES) relied on external funding sources in order to hold meetings such as the one in Paris. However, it was certainly not a condition that funding came from Sanofi Pasteur MSD.
5 The allegations relating to the public health expert were not made about Sanofi Pasteur MSD. Indeed, as it would demonstrate later, what was described was not at all familiar to Sanofi Pasteur MSD.
6 The Paris meeting addressed the desire to eradicate cervical cancer worldwide through the combination of improved education, screening, treatment and implementation of vaccination. Sanofi Pasteur MSD submitted that the meeting in Paris addressed this in a holistic and balanced way.
7 The travel and hospitality arrangements for the Paris meeting were Code compliant and certified as such.

The first part of the article on page 6 of The Guardian contained various allegations made by a public health expert. None of the allegations were specifically about Sanofi Pasteur MSD: the article referred to 'drug firms' and 'pharmaceutical companies'. Sanofi Pasteur MSD was not the only company active in the HPV vaccine field.

Prior to the licensing of Gardasil, Sanofi Pasteur MSD had the following contact with the expert:

July 2004	One to one meetings between her and Sanofi Pasteur MSD's medical director regarding cervical cancer and HPV vaccine. At this meeting, her considerable experience in the area of cervical screening was noted. She was therefore highlighted as a potential member of a future advisory board, a fact that was mentioned to her at the meeting.
June 2005	Invitation from an agency working on behalf of Sanofi Pasteur MSD to her to participate in an advisory board meeting 'to discuss the clinical, service and funding issues related to the introduction of HPV vaccines into the NHS'. An honorarium of £500 was offered. She declined the invitation.
October 2005	Letter sent by her to her local Sanofi Pasteur MSD healthcare development executive. At that time, healthcare development executives were making appointments with those in primary care trusts responsible for making policy decisions on budgets. Her local healthcare development executive had sought appointments with the three people copied in on this letter (a director of public health and two heads of medicines management) who had notified her, prompting this letter.
October 2005	Telephone call to her secretary by her local healthcare development executive to enquire about an appointment (following the recommendation of other policy makers in that locality). At that time her letter of 17 October 2005, which had been sent to head office, had not been seen by the healthcare development executive. The secretary advised that the response would be clear from the letter and no appointment was made.

Since Gardasil was licensed in September 2006, Sanofi Pasteur MSD had had the following contact with her:

December 2006 Letter sent to her by Sanofi Pasteur MSD's medical director, responding to a position statement on HPV vaccine she had co-authored. Of particular note was that this letter addressed claims she had made about the activities of pharmaceutical representatives. It stressed that all activities undertaken by Sanofi Pasteur MSD were reviewed to ensure compliance with the Code. Sanofi Pasteur MSD sent her a copy of the PMCPA leaflet describing the Code for health professionals and asked her to contact it if she suspected the company's activities were not Code compliant.

January 2007 Letter sent to Sanofi Pasteur MSD's medical director by her, responding to his letter of December 2006. In her response she welcomed the reassurances Sanofi Pasteur MSD had provided, to the extent that she did not feel a meeting to discuss the matter further was necessary. Sanofi Pasteur MSD therefore considered that the issue had been satisfactorily resolved.

In light of these details, Sanofi Pasteur MSD was surprised and disturbed to read the allegations made in The Guardian. With specific reference to Clause 18.1, she received one invitation to participate in an advisory board long before Gardasil was licensed. As part of this invitation she was offered £500 as compensation for the time she would have spent participating in the meeting. Advisory board meetings were a legitimate activity within the Code. The invitation gave no indication, either directly or implied, that its purpose was an inducement to prescribe, supply, administer, recommend, buy or sell any medicine. This was a non-promotional activity conducted prior to Gardasil being licensed or becoming available. Sanofi Pasteur MSD therefore refuted a breach of Clause 18.1.

Referring to Clause 12.2, she had received no promotional mailings for Gardasil from Sanofi Pasteur MSD. It therefore had exercised restraint on the frequency and volume of promotional material distributed and denied a breach of Clause 12.2.

Sanofi Pasteur MSD noted that the First Global Summit on Cervical Cancer was held on 22 March 2007 at the United Nations Educational, Scientific and Cultural Organization (UNESCO) in Paris. As correctly stated in the article, the meeting was organised by CES. Financial support was provided by Sanofi Pasteur MSD headquarters in France.

The objective of the meeting, which was endorsed by UNESCO and the International Federation of Gynaeco-Oncology (FIGO) and held under the high patronage of the French President and the patronage of the French Minister of Health, was to continue the fight against cervical cancer. It built on three previous events, none of which was sponsored by Sanofi Pasteur MSD:

- the 'Charter of Paris Against Cancer' signed in February 2000 at the first World Summit Against Cancer organised by UNESCO;
- the World Cancer Declaration adopted at the World Cancer Congress in Washington, July 2006;
- the 'Call of Rabat' in September 2006 which developed a policy to prevent cervical cancer in developing countries supported by the Queen of Morocco and UNESCO ambassador.

One part of the meeting to create a Coalition On Cervical Cancer formed of global and European figureheads to sign 'The Charter Against Cervical Cancer', setting out the participants' commitment to place cervical cancer high on the global health agenda. The organisation was overseen by a Scientific Committee comprised of relevant experts. The Scientific Committee, drew up an agenda to address the worldwide management of cervical cancer in a holistic and balanced way. The first part of the agenda therefore covered all aspects of the disease from its impact, treatment options, through to prevention by both screening and vaccination. The second part was focussed on defining actions for the future, which included education of health professionals and patients, as well as the role of policy makers. The agenda was certified as compliant with the Code. The slides presented further reinforced the holistic nature of the agenda. Vaccination was referred to in the context of the goal of eradication of cervical cancer and Gardasil was not mentioned by name. Indeed, the existence of two vaccines was explicit. No promotional materials for Gardasil were available at the meeting. The agenda was accurate, balanced, fair, objective, unambiguous, reflected the current state of knowledge of cervical cancer management and was not misleading. Sanofi Pasteur MSD therefore refuted a breach of Clause 7.2.

Prior to the main meeting there was a breakfast briefing for UK journalists. This was an informal session where journalists could speak about management of cervical cancer with a panel of UK experts who were present for the Global Summit. The majority were speakers during the main meeting. The session was facilitated by Sanofi Pasteur MSD UK.

Invitations to potential delegates from the UK were extended to relevant policymakers, health professionals, patient organisations and journalists. The invitation supplied by the organisers was reviewed under the Code and following this review, a UK version was certified. It was clearly mentioned in both versions that the meeting was sponsored by Sanofi Pasteur MSD. In the certified version, the sponsorship statement was included at the start and the end of the letter. The certified version was used by the UK agency that invited UK journalists. Due to a clerical error, the French agency, responsible for inviting other UK delegates, used the original version.

Copies of the invitee and attendee lists were provided. With the exception of freelance journalists and speakers, attendees (including the sportswoman from the UK) were not paid to attend the meeting. If necessary, economy air or standard class rail travel, and overnight accommodation were offered. These arrangements were certified as compliant with the Code. The speakers from the UK were two health professionals (one chairman, one speaker), one patient group representative and one patient. The health professionals were offered an honorarium but not the patient group representative or the patient. In summary, the meeting was held at an appropriate venue; travel was economy or standard class, hospitality was provided in the context of the meeting, was secondary to it and was of subsistence level. Sanofi Pasteur MSD therefore refuted a breach of Clause 19.1.

The fact that the meeting was sponsored by Sanofi Pasteur MSD was clearly stated in the invitation letter sent to the invitees in advance of the meeting. From the outset invitees were aware that the meeting was sponsored by Sanofi Pasteur MSD. Sanofi Pasteur MSD noted that the articles in The Guardian did not allege that the sponsorship was disguised. The company therefore refuted a breach of Clause 19.3. A copy of the delegate pack was provided; this was produced by the conference organisers and did not carry a sponsorship statement. When delegates entered the building, as well as the delegate pack they also received a document in French detailing the agenda and members of the Coalition; this was a requirement of the President's office.

Freelance journalists were not incentivised to attend the meeting. However, due to their employment status, they could claim expenses corresponding to 1.5 times their daily rate. These journalists signed an agreement acknowledging that they were remunerated by Sanofi Pasteur MSD for their time spent at the meeting and that the company waived the right to review any article that might arise from them having attended the meeting.

Representatives of patient groups were treated in the same way as all other attendees (with the exception of freelance journalists) with respect to travel, accommodation and lack of payment to attend. No specific activities were conducted with patient groups other than their being invited to the meeting. Sanofi Pasteur MSD therefore refuted a breach of Clause 20.3.

Logistical support was provided by four agencies, three in France and one in the UK.

In summary, Sanofi Pasteur MSD denied breaches of Clauses 18.1, 12.2, 7.2, 19.1, 19.3 and 20.3. All contact with the public health expert had been Code compliant. The Paris meeting was organised by a third party and sponsored by Sanofi Pasteur MSD, a fact that was clear from the outset and was not challenged in The Guardian. The meeting was endorsed by a number of highly respected organisations and its content was balanced, addressing multiple areas relating to the management of cervical cancer, not only vaccination.

As previously noted the two articles contained multiple inaccuracies and misrepresented the purpose and content of the meeting. Sanofi Pasteur MSD reviewed the arrangements for the meeting to ensure they were suitable and certified the documents to be supplied to UK delegates prior to the meeting, as well as the arrangements for travel and accommodation. Sanofi Pasteur MSD had maintained high standards at all times and had not reduced confidence in the pharmaceutical industry. It therefore also refuted breaches of Clauses 9.1 and 2.

In response to a request for further information Sanofi Pasteur MSD stated that the agenda for the advisory board meeting was provided at the meeting, not with the invitation. Since the expert did not attend the meeting she would therefore not have received a copy of the agenda. A copy of the evaluation form was provided.

With respect to the First Global Summit on Cervical Cancer, the revised invitee and attendee lists, including the additional information requested, were provided.

The First Global Summit on Cervical Cancer focussed on the worldwide management of cervical cancer in a holistic and balanced way. As an introduction to the day's events, Sanofi Pasteur MSD gave journalists from the UK and Ireland the opportunity to question a panel of UK experts in the field of cervical cancer, two of whom were speaking at the event. The meeting was held from 8 to 9am over breakfast. The concept and arrangements for the meeting were certified as Code compliant. The panel consisted of three experts rather than the five initially envisaged. The journalist who had written the articles in The Guardian did not attend the breakfast meeting.

In order to ensure Code compliance in a question and answer based forum, the meeting was facilitated by the Senior Medical Adviser, Sanofi Pasteur MSD, who was a registered Code signatory. She introduced the meeting, placing it within the context of the First Global Summit on Cervical Cancer, declaring the company's sponsorship of the event and explaining that the purpose of the meeting was to allow journalists to ask questions of the three UK expert participants and Summit speakers.

As the meeting was an introduction to the Summit, for which delegate materials were available, no additional materials were distributed at the breakfast meeting. No PowerPoint presentations were given; as a member of the Scientific Committee and chair of the Summit session on impact of the disease, one panellist was asked to present the background to the First Global Summit on Cervical Cancer. The two others were asked to introduce themselves by summarising their professional backgrounds in the field of cervical cancer. The journalists were then able to ask the Panel questions relating to cervical cancer prevention. All attendees went on to attend the meeting at UNESCO at 10am.

PANEL RULING

The Panel noted that it had asked Sanofi Pasteur MSD

to respond, *inter alia*, to Clauses 9.1 and 2 in relation to each matter and to the cumulative effect of the matters raised in the articles. The company had only responded to Clauses 9.1 and 2 cumulatively but not in relation to each matter. The Panel noted that the company had been given an opportunity to respond to each matter in relation to Clauses 2 and 9.1 in accordance with the Constitution and Procedure and it would thus rule on that basis.

The Panel noted Sanofi Pasteur MSD's submission that The Guardian article referred to 'drug firms' and 'pharmaceutical companies'. The Panel agreed that the section referring to the public health expert's views did refer to drug firms and pharmaceutical companies. The heading on the front page was 'Vaccination campaign funded by drug firm'. Sanofi Pasteur MSD was named in relation to the meeting in Paris. The only mention of GlaxoSmithKline, which was developing another vaccine, was in relation to whether money was sought from GlaxoSmithKline and the reply was that GlaxoSmithKline had not been approached.

The Panel also noted that there was some confusion as to whether the summit was '… on Cervical Cancer' or 'against Cervical Cancer'. The programme and documentation referred to the meeting as 'First Global Summit on Cervical Cancer'.

The Panel noted that the article headed 'Alarm at "battering ram" tactics over cervical cancer' referred to the invitation of the public health expert and others to meetings which they would be paid £1,000 to attend and to the number of letters received from representatives. The Panel noted that the comments related to the activity of more than one company. Nonetheless, Sanofi Pasteur MSD and Gardasil was the only company and product identified and thus that company was asked to respond to these comments.

The Panel noted it was acceptable for companies to arrange advisory board meetings and the like and to pay health professionals and others for advice on subjects relevant to their products. Nonetheless, the arrangements for such meetings had to comply with the Code. The choice and number of delegates should stand up to independent scrutiny. Each should be chosen according to their expertise such that they would be able to contribute meaningfully to the purpose and expected outcomes of the meeting. The number of delegates at a meeting should be limited so as to allow active participation by all. The number of meetings and the number of delegates at each should be driven by need and not the invitees' willingness to attend. Invitations to participate in an advisory board meeting should state the purpose of the meeting and the expected advisory role and amount of work to be undertaken. If an honorarium was offered it should be clear that it was a payment for such work and advice and not a payment to attend a promotional meeting. Honoraria must be commensurate with the time and effort involved and the professional status of the recipients.

The Panel noted that Sanofi Pasteur MSD invited the public health expert to participate in an advisory board in June 2005. The invitation described the advisory board as a multidisciplinary advisory panel of NHS stakeholders to discuss clinical, service and funding issues relating to the introduction of HPV vaccines into the NHS. The agenda would run from 11am to 4pm. An honorarium of £500 would be paid and all travelling expenses reimbursed. Confidentiality agreements would be signed. The Panel queried whether the invitation made the amount of work required sufficiently clear given that invitees were not sent a copy of the agenda at this stage. The Panel noted that the final agenda ran from 10.30am to 4pm and provided plenty of opportunity for participation and discussion. The Panel considered that the agenda was not unreasonable given the stated purpose of the meeting. Overall the Panel considered that the honorarium of £500 to participate in the advisory board as described in the invitation was not unreasonable. The invitation made the role of participants sufficiently clear. The Panel noted the amount of work actually required. The payment was for genuine services. It was not inappropriate to offer to pay attendees of the advisory board in question. No breach of Clause 18.1 was ruled. The Panel accordingly ruled no breaches of Clauses 9.1 and 2.

In relation to the number of letters from representatives, the Panel noted Sanofi Pasteur MSD's submission that the public health expert had received no promotional mailings for Gardasil. The Panel noted that a Sanofi Pasteur MSD healthcare development executive had contacted three people within her local PCT responsible for policy decisions on budgets to make appointments. The expert had replied in a letter dated 17 October to the individual concerned, via the company's head office, explaining that a meeting was not necessary given the PCT's current position on vaccination policy. Despite this letter the Panel was concerned that some eight days later the same healthcare development executive sought an appointment with the expert, the company not having forwarded a copy of the expert's earlier letter. The company also noted that subsequent to the grant of the marketing authorization in September 2006 Sanofi Pasteur MSD's medical director wrote to her about a position statement on HPV vaccine which she co-authored. The position statement had advised staff to decline invitations to see company representatives. No one company was identified. She responded stating that she was reassured by Sanofi Pasteur MSD's response.

Overall the Panel did not consider that the volume of mailings sent by Sanofi Pasteur MSD was unacceptable. No promotional mailings about Gardasil had been sent to the expert. Nor was the frequency of contact made by healthcare development executives unacceptable. The Panel ruled no breach of Clauses 2, 9.1 and 12.2.

In relation to the meeting held in Paris on 22 March the first thing that the Panel had to consider was whether it or any aspect of it came within the scope of the Code. The meeting was held in France and was sponsored by Sanofi Pasteur MSD's French headquarters. The article 'Vaccination campaign funded by drug firm' noted the

President of CES, a public health institution stated that she agreed to participate only on condition that Sanofi Pasteur MSD paid. The response from the company stated that the meeting was organised by CES – implying that CES had more than a participatory role. The position was unclear. The Panel noted that the agenda featured both European and non European (US and South American) speakers and addressed global issues in relation to cervical cancer. Twenty five UK delegates attended (11 health professionals, 13 journalists and 1 representative from a patient group). The presentations were directed to all the delegates; no material was presented during the main agenda which solely addressed a UK audience. The Panel also considered that the supplementary information to Clause 1.7 Applicability of Codes was relevant. The Panel noted that a breakfast meeting had been held solely for UK journalists. The Panel considered that the Code applied to the invitation and the hospitality (accommodation, travelling and subsistence) provided to UK delegates. The Panel considered that the Code also applied to all of the arrangements in relation to and content of the breakfast briefing.

The Panel noted that the breakfast briefing, organised by Sanofi Pasteur MSD UK and attended by journalists from the UK and Ireland, enabled delegates to question a panel of UK experts in the field of cervical cancer. It was chaired by a medical adviser from the UK company. The Panel did not have a copy of the invitation to the breakfast briefing. No PowerPoint presentations were made and nor were any additional materials made available. The Panel considered that it had no evidence to show on the balance of probabilities that either the discussions that took place or the arrangements were unacceptable in relation to Clauses 2, 7.2, 9.1, 19.1 and 19.3.

The Panel noted that the arrangements for UK delegates should comply with Clause 19. The 2006 edition of the Code extended the requirements of Clause 19 to apply to journalists and patient groups for the first time. The Panel noted that travel was economy or standard class rail travel. The meeting venue did not appear unreasonable. Overnight accommodation was offered. It was unclear how many UK delegates had been provided with accommodation. Overall the Panel did not consider that the accommodation, travel and subsistence provided were unacceptable in relation to the requirements of Clause 19.1.

The Panel noted that UK journalists had been provided with a certified invitation by a UK agency. Due to human error UK health professionals and others had been invited using an uncertified version of the invitation by a French based agency. The uncertified two page invitation only referred to the company sponsorship at the end, as a postscript. Clause 19.3 required sponsorship to be declared such that the reader was aware of it at the outset. A breach of Clause 19.3 was ruled in relation to the invitation to UK health professionals and others.

The Panel noted that UK freelance journalists were paid a fee for attendance of 1.5 times their daily rate. The Panel noted that the supplementary information to Clause 19.1 stated that funding must not be offered to a health professional to compensate them merely for the time spent in attending meetings. The supplementary information to Clause 20.2 stated that meetings organised for or attended by, *inter alia*, journalists should comply with Clause 19. The Panel noted that there were differences in the role played at such meetings by journalists and health professionals. There were situations where it was legitimate to pay a health professional or journalist for their time when attending meetings such as participation on advisory boards or when they were otherwise being employed to undertake a specific piece of work so long as in each case the arrangements as a whole complied with the Code. On the evidence before the Panel it appeared that the journalists were simply delegates; they were not being paid for the benefit of their expertise or to undertake a specific piece of work. In such circumstances the payments were inappropriate in relation to Clause 19.1. Their freelance status was irrelevant. A breach of Clause 19.1 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 for particular censure.

The Panel, noting its rulings above, did not consider that the cumulative effect of the allegations was sufficient to warrant a ruling of a further breach of Clause 9.1 or a breach of Clause 2.

The Panel considered that all of its rulings applied to both Case AUTH/1980/3/07 and Case AUTH/1983/3/07.

Case AUTH/1980/3/07

Proceedings commenced	**28 March 2007**
Case completed	**28 June 2007**

Case AUTH/1983/3/07

Complaint received	**29 March 2007**
Case completed	**28 June 2007**

PHARMACIST PRACTITIONER v SANOFI-AVENTIS

Conduct of representative

A pharmacist practitioner at a general practice complained that, during the course of promoting Lantus (insulin glargine) and Acomplia (rimanobant), a representative from Sanofi-Aventis displayed an apparent lack of knowledge about the data.

The representative claimed that a flowchart from the American Diabetic Association (ADA) advised the use of basal insulins such as Lantus second line to metformin in type 2 diabetics. The complainant had since found this flowchart online; those present were not allowed a close look at this information at the meeting. While this was a recommendation, it was actually one of the three interventions advised. The same page as the flowchart stated 'Early initiation of insulin would be a safer approach for individuals presenting with weight loss, more severe symptoms, and glucose values >250-300 mg/dl'. This was not the impression given by the representative; it was intimated that basal insulins were being recommended in this advice as second line to metformin for all type 2 diabetics.

Of greater concern was the information given about Acomplia. Again the representative presented information that was not passed around or left to allow a closer look but the complainant was certain that the data came from the RIO-Diabetes study. However, the representative wrongly stated that the patients were newly diagnosed and treatment naïve when in fact all had been on oral therapy for 6 months in randomisation. Conversely, the SERENADE study was conducted in treatment naïve diabetics, however the trial was currently unpublished and the indication studied remained unlicensed. It seemed that the representative was confused about these separate studies and had presented data from the two as if they were one and the same.

The representative then stated that other practices were, based on these data, using Acomplia as a third line hypoglycaemic in diabetics, in place of glitazones. Acomplia was not licensed as a hypoglycaemic and he did not think it should be promoted on this basis.

Further comments were sought from the complainant on receipt of the company's response. The complainant was not questioning the use of ADA/ESAD guidelines in general but the way that they were presented. The flowchart clearly indicated three treatment alternatives and that only one of these was discussed, without making it clear there were three, misrepresented the data.

The complainant noted that Sanofi-Aventis had submitted that the data were presented in line with the current marketing authorization and not presented in relation to diabetes. Despite this assertion the detail aid made it very clear that the SERENADE study was conducted in overweight patients with type 2 diabetes who were inadequately controlled! Additionally, in discussion the representative specifically referred to patients with diabetes (following on from the discussion about Lantus) and diabetes medicines. The complainant considered that the detail aid implied that Acomplia could be used as an agent to reduce HbA_{1C}.

The complainant had left the meeting and returned to hear the representative talking about the use of Accomplia instead of glitazone. He therefore sought clarification of the representative's comments whereupon he was told that Acomplia could be used in place of hypoglycaemics and in fact this was being done in other practices locally. The clarification the complainant sought was based on his surprise that Acomplia was apparently touted as an alternative to hypoglycaemics. At no time did the representative mention that such use would be outside the marketing authorization nor did he state that Sanofi-Aventis could not support such use.

Finally, the complainant advised that three other health professionals (a diabetes practice nurse and two doctors) were also present at the meeting and all three had stated that the representative had left them with the impression that Acomplia could be used to reduce HbA_{1C} in type 2 diabetics.

The Panel noted that the guideline as shown in the Lantus detail aid clearly detailed three treatment options for patients who failed to reach an HbA_{1C} target of >7% namely; 'Add basal insulin - most effective'; 'Add sulphonylurea - least expensive'; or 'Add glitazone - no hypoglycaemia'. The Panel noted the representative's statement that 'At no point… did I state or imply that basal insulin was the only option available to them, I clearly stated that it was another option available'. The representatives' briefing material however recommended that representatives focused on the left hand side of the page (the basal insulin option) and led discussion around the positioning of basal insulin. Nonetheless there was no implication in the briefing material that basal insulin was the only option mentioned in the guideline; it was referred to as 'a treatment'. The Panel also noted that the representative also denied that he had intimated that basal insulins were recommended as second line treatment to metformin for all diabetics. The Panel considered that it was impossible in such circumstances to determine on the balance of probabilities exactly how the guideline had been presented. No breach of the Code was thus ruled.

The Panel noted each party's submission in relation to the Acomplia data. The representative stated that he had made it clear that he was discussing the SERENADE data and not the RIO-Diabetes study. The Acomplia detail aid clearly referred to the SERENADE study. It appeared that the complainant was concerned that he in error had referred to the RIO-Diabetes study but that this error had not been corrected by the representative. It was impossible to determine on the balance of probabilities what had been said and the Panel thus ruled no breach of the Code.

The Panel noted that Acomplia was licensed 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. The Panel noted that the detail aid referred to overweight patients. The relevant representatives' briefing material began 'Identify overweight patients with type 2 diabetes as the patient group we would like to discuss'. This was not unacceptable. Again the Panel considered that it was impossible to determine on the balance of probabilities exactly what had been said and ruled no breach of the Code.

The Panel noted that according to both parties the discussion of Acomplia had included mention of glitazones. Both parties also agreed that the complainant had asked a question about this matter. However the parties' accounts differed. In addition the complainant had been absent for the beginning of the relevant discussion and had returned during a discussion about the use of Acomplia instead of a glitazone and had sought clarification of the representative's comments. The complainant did not provide his understanding of how this discussion had started. According to Sanofi-Aventis in response to a question about Acomplia and diabetics the representative explained that local practices used Acomplia in type 2 diabetics in whom weight loss was appropriate. Thereafter, when asked if it was being used in place of other medicines the representative stated that some local practices had used Acomplia in place of a glitazone. The Panel did not accept the company's suggestion that it could rely on the exemption to the definition of promotion set out in the Code. If the company's version of the discussion was correct it did not appear that the representative had necessarily been asked about replacement of glitazone with Acomplia.

The Panel noted that representatives could respond to unsolicited questions about the unlicensed use of their products so long as the criteria set out in the supplementary information were satisfied. Representatives should be extremely cautious when responding to such requests. It was difficult for representatives to satisfy the criterion given their role, particularly at a group promotional meeting. Attendees were likely to view the representatives' comments in the context of promotion. The safest course of action was to forward such requests to the company's medical information department.

Whilst there were some similarities the parties' accounts differed. In particular the complainant was absent at the beginning of the relevant discussion. It was not possible to determine on the balance of probabilities exactly what had been said and thus the applicability of the exemption to the definition of promotion. No breach of the Code was ruled.

A pharmacist practitioner at a general practice complained about the conduct of a representative from Sanofi-Aventis.

COMPLAINT

The complainant stated that during the course of discussions with a representative of Sanofi-Aventis about Lantus (insulin glargine) and Acomplia (rimanobant) he was amazed by the apparent lack of knowledge that the representative possessed about data and evidence behind these products.

With respect to Lantus, the representative briefly showed a flowchart from the American Diabetic Association (ADA) and claimed that this advised the use of basal insulins such as Lantus second line to metformin in type 2 diabetics. The complainant had since found this flowchart online; those present were not allowed a close look at this information at the meeting. While this was a recommendation, it was actually one of three interventions advised. The text on the same page as the flowchart also stated 'Early initiation of insulin would be a safer approach for individuals presenting with weight loss, more severe symptoms, and glucose values >250-300 mg/dl'. This was not the impression given by the representative; in fact it was intimated that basal insulins were being recommended in this advice as second line to metformin for all type 2 diabetics.

Of greater concern was the information given about Acomplia. Again the representative presented information that was not passed around or left to allow a closer look but the complainant was certain that the data came from the RIO-Diabetes study. The representative presented these data showing statistically significant reductions in body weight, waist circumference and improvements in other biological markers including HbA_{1C} and cholesterol. However, he wrongly stated that the patients were newly diagnosed and treatment naïve when in fact all had been on oral therapy for 6 months in randomisation. Conversely, the complainant knew that the SERENADE study was conducted in treatment naïve diabetics, however the trial was currently unpublished and the indication studied remained unlicensed. It seemed that the representative was confused about these separate studies and had presented data from the two as if they were one and the same.

The representative then stated that other practices were, based on these data, using Acomplia as a third line hypoglycaemic medicine in diabetics, in place of glitazones. To the complainant's knowledge, and having referred to the current summary of product

characteristics (SPC), he did not believe that Acomplia was licensed as a hypoglycaemic and he did not think it should be promoted on this basis.

The complainant was greatly concerned about several aspects of this meeting:

- that Acomplia was apparently being promoted outside its existing licence;
- the representative's lack of knowledge and the confused messages about the indications, licence and evidence for his products;
- the representative's lack of knowledge about the Code which explicitly forbade off-licence promotion and demanded high quality.

When writing to Sanofi-Aventis the Authority asked it to respond in relation to Clauses 3.2, 7.2 and 15.2 of the Code.

RESPONSE

With regard to the promotion of Lantus the representative confirmed that he presented from the approved materials and spoke in accordance with the training and written materials that he had received to support these. He was also clear that the complainant asked only one question of clarification during the meeting. Sanofi-Aventis considered that many of the issues raised by the complainant might have been avoided had clarification been sought at the time. Although no material used was left with the complainant, had he requested additional information on the items discussed, this would have been provided.

The complainant had questioned the appropriateness of the use of the ADA/European Association for the Study of Diabetes (EASD) guidelines to support the product's use in type 2 diabetics. This flowchart had been faithfully reproduced from the original published in 2006 and was clearly referenced in the detail aid. The original guideline defined the joint position of the two large diabetes medical associations on the optimal treatment of hyperglycaemia in type 2 diabetics. However, the complainant had not identified this article correctly, and his comments referred to a separate article which referred to this flowchart, rather than to the actual guidelines. Had he asked for the reference, this would have been provided through Sanofi-Aventis' medical information service.

The original guidelines (as referenced in the detail aid) indicated that 'Insulin is the most effective of diabetes medications in lowering glycaemia', and advocated 'Early addition of insulin therapy in patients who do not meet target goals' (ie in the group under consideration). Whilst not disregarding the quotation that the complainant had included from elsewhere, the guidelines were very clear that all patients not at target should be considered for insulin therapy. The poorly controlled group of patients that the complainant referred to was included in the original guidelines, but rather than the statement quoted in error by the complainant that in these patients insulin was a safer choice, the guidelines were more proscriptive in directing that in such 'severely uncontrolled' patients, 'insulin is the treatment of choice', as it was the only agent capable of achieving the rapid control of the disease that was essential. Sanofi-Aventis considered therefore that it was consistent with the guidelines that insulin be considered for all patients above target levels of glycaemic control.

Turning to the representative's use of the flowchart, his role was not to promote the guidelines as such, but to indicate where in the guidelines use of Lantus was appropriate. He recalled that he correctly pointed out that a basal insulin (such as Lantus) was an appropriate choice in these patients. As above, Sanofi-Aventis considered that this did not misrepresent the intent of the original guidelines, and that placing Lantus within this context was appropriate promotion in terms of where in practice the product could be used. This was consistent with the training and briefing material that the representative had received.

With regard to the promotion of Acomplia, Sanofi-Aventis noted that the complainant had wrongly identified the study that was discussed during the meeting and his comments about the RIO-Diabetes study were therefore in relation to an incorrect reference. Again, had he asked for clarification at the meeting, the study would have been identified as the SERENADE study. The complainant's comments about the representative misrepresenting the data were therefore confounded by this error. The representative's description of the patient population was correct and consistent with the promotional information - the study was performed in patients with untreated type 2 diabetes, not those who had received oral therapy for at least 6 months. It was clear that the representative made an accurate representation of the materials available to him; any confusion had arisen from the complainant's subsequent misinterpretation and this could easily have been resolved through enquiry at the time of the discussion.

The complainant then questioned the appropriateness of the inclusion of data from the SERENADE study in support of Acomplia, noting that this was in the treatment of diabetes, an unlicensed indication. Whilst the study examined an unlicensed indication, the data used to support Acomplia were restricted to, and entirely consistent with, that which was relevant to the marketing authorization. Specifically, this study was not presented in relation to the treatment of diabetes; the effects demonstrated were limited to those contained within the product licence, namely the effects on obesity (weight and waist circumference) and its associated risk factors (glycaemic control and HDL-cholesterol and triglyceride levels). Likewise, the data presented was that of a subset of patients in the study with a body mass index (BMI) >27kg/m^2, deliberately so as to be in accordance with the marketing authorization. As this study was not yet published, the referenced data on file that supported its inclusion was provided. This was freely available on request and was limited to the particulars of the marketing authorization described above so as to avoid the impression that this study was being used to prompt enquiries on an unlicensed indication.

Finally, it was reported that the representative had referred to the use of Acomplia in other local practices. In this regard the representative clearly remembered that in response to the complainant asking where Acomplia fitted in the treatment of diabetes he had replied that local practices used Acomplia in patients with type 2 diabetes in which weight loss was considered to be appropriate. The complainant then asked if it was being used in place of other medicines, to which the representative replied that some local practices used Acomplia in place of a glitazone. Sanofi-Aventis considered that it was clear that this information was specifically solicited by the complainant and as such the representative had acted appropriately in responding to the request by sharing his knowledge. Providing such information in response to a direct request would be expected; the complainant appeared to have confused this with unsolicited promotion.

In summary, Sanofi-Aventis believed the representative was well informed, well trained and conscientious and he had consistently performed to high standards. It was clear that the representative had used his materials appropriately during his meeting with the complainant, and that these and associated briefing materials were consistent with the requirements of the Code.

Sanofi-Aventis considered that high standards had been maintained throughout and, in particular, that breaches of Clauses 3.2, 7.2 and 15.2 had not occurred.

The response from Sanofi-Aventis was sent to the complainant and his comments invited.

COMMENTS FROM THE COMPLAINANT

The complainant considered that Sanofi-Aventis' response highlighted that the complaint questioned the appropriateness of the use of the ADA/EASD guidelines in the promotion of Lantus. The complainant believed the comment had been misconstrued. He had not questioned the use of these guidelines in general but the way that they were presented. The flowchart provided clearly indicated three treatment alternatives (basal insulin, sulphonylurea or glitazone) for patients failing to reach an HbA_{1C} target of 7% or below while implementing lifestyle interventions and taking metformin. Each intervention was indicated with an advantage (most effective, least expensive and no hypoglycaemia respectively). Treatment choice within the NHS was therefore a clinical decision based on the patients' condition and an assessment of the cost-efficacy of each option with consideration of currently available resources.

That only one of the treatment options was discussed without it being made clear that there were three misrepresented the data. Additionally, while the complainant accepted that the reference was detailed in the promotional aid he noted again that, on the day, those present were not allowed closer examination of the material nor were they left with a copy. It was clear that the representative was not intent on leaving any information behind.

Finally, with respect to the discussion about Accomplia, the complainant noted that in his complaint he had raised the RIO-Diabetes Study. Sanofi-Aventis's response correctly noted that the data represented were from the SERENADE study and not the RIO-Diabetes study. The complainant was surprised that the representative did not correct him when he raised the RIO-Diabetes study during the discussion, even more so given that the detail aid made several references to the SERENADE study as a source for the data. Apparently, the representative was not aware of this or chose to ignore this fact in the conversation.

The complainant noted that Sanofi-Aventis had submitted that the data were presented in line with the current marketing authorization and not presented in relation to diabetes. Despite this assertion the detail aid made it very clear that the SERENADE study was conducted in overweight patients with type 2 diabetes who were inadequately controlled! Additionally, in discussion the representative specifically referred to patients with diabetes (following on from the discussion about Lantus) and diabetes medicines. The complainant also noted page headings in the detail aid which read 'In overweight patients with type 2 diabetes…' and 'Acomplia significantly improves HbA_{1C} compared with placebo' respectively. As these pages were adjacent to each other, the complainant considered that this left the casual reader with the impression that Acomplia could be used to reduce HbA_{1C}. This became even more apparent when comparing the briefing document (prepared in February 2007) with the actual detail aid (prepared in March 2007) from which it would be noted that the claim 'Acomplia significantly reduces weight and waist circumference compared to placebo' had been dropped from the blue header areas in the detail aid. Had this been left in the header area perhaps the detail aid would be less likely to mislead readers.

The complainant noted that the representative claimed he made specific queries about what other practices were doing and where they were using Acomplia in patients with type 2 diabetes. The complainant stated that he must make it clear that he had left the meeting and returned to hear the representative talking about the use of Accomplia instead of glitazone. He therefore sought clarification of the representative's comments whereupon he was told that Acomplia could be used in place of hypoglycaemics and in fact this was being done in other practices locally.

The complainant would never allow his clinical practice to be steered by what other practices were doing. The practice was steered by evidence-based medicine and the complainant was therefore not interested in what other surgeries were doing. The clarification the complainant sought was based on his surprise that Acomplia was apparently touted as an alternative to hypoglycaemics. Furthermore, the complainant had previously noted that representatives always handled conversations about off licence usage very cautiously. It was normal during this type of

discussion to be reminded several times that the company, based on the current marketing authorization, could not endorse such use of the medicine. At no time did the representative mention that such use would be outside the marketing authorization nor did he state that Sanofi-Aventis could not support such use.

Finally, the complainant advised that a diabetes practice nurse and two doctors were also present at the meeting. The complainant had discussed Sanofi-Aventis' response with them, with a view to providing as detailed a response as possible. All three had stated that the representative had left them with the impression that Acomplia could be used to reduce HbA_{1C} in patients with type 2 diabetes. This was particularly clear in their minds as all three of them were confused by this marketing message as they knew Acomplia was licensed as an adjunctive treatment for obesity, not a recognised hypoglycaemic.

FURTHER COMMENTS FROM SANOFI-AVENTIS

Sanofi-Aventis was disappointed that only now the complainant made it known that he was not present for the entire duration of the meeting – this added considerable confusion as to how his perception of the discussion might have been affected. Specifically, the representative was very clear that he placed the Acomplia information in the context of the SERENADE study, which the complainant appeared to be disputing despite the fact that he missed part of the discussion.

Finally, the complainant questioned the impression that Acomplia could be used to 'to reduce HbA_{1C} in patients with type 2 diabetes.' Sanofi-Aventis noted that the marketing authorization for the product stipulated the primary effect as weight loss but included this additional benefit for patients BMI>27kg/m^2 with type 2 diabetes and had acknowledged that promotion of these benefits in addition to the effects on weight was consistent with the marketing authorization. Discussion in this context was not 'use outside the marketing authorization' as the complainant alleged. The promotional campaign for Acomplia positioned the product on this basis – weight loss was always positioned as the primary effect in all materials and any additional effects on risk factors were positioned second to these and always shown in conjunction with the primary effect. The complainant was very clear after the meeting that all staff were aware of the product's primary effect as a treatment for obesity indicating that promotion was effective at conveying this message. It appeared that the impression left of the effect on glycaemic control was additional to the effects on weight rather than in isolation, which remained consistent with the marketing authorization and the promotional campaign, which the representative had very clearly indicated in his comments above.

PANEL RULING

The Panel noted that the complaint had been submitted promptly; the meeting took place on 19 April, the complaint was dated 20 April and was received by the Authority 4 days later. Although each party should therefore have a relatively good recollection of the meeting at issue, it was of concern that accounts differed. The Panel noted that the complainant had been absent for part of the meeting.

The Panel noted the complainant's allegation that during the discussion on Lantus, only one of the three treatment options featured on the ADA/EASD guideline had been discussed and it was not made clear that there were three options. Further the complainant alleged that the representative implied that basal insulin was recommended in the guidelines as second line treatment for all diabetics. The Panel noted that the guideline as shown in the Lantus detail aid clearly detailed three treatment options for patients who failed to reach an HbA_{1C} target of >7% namely; 'Add basal insulin - most effective'; 'Add sulphonylurea - least expensive'; or 'Add glitazone - no hypoglycaemia'. The Panel noted the representative's statement that 'At no point during the Lantus discussions regarding ADA/EASD guidelines did I state or imply that basal insulin was the only option available to them, I clearly stated that it was another option available'. The representatives' briefing material however recommended that representatives focused on the left hand side of the page (the basal insulin option) and led discussion around the positioning of basal insulin. Nonetheless there was no implication in the briefing material that basal insulin was the only option mentioned in the guideline; it was referred to as 'a treatment'. The Panel also noted that the representative also denied that he had intimated that basal insulins were recommended as second line treatment to metformin for all diabetics. The Panel noted the parties' submissions on this point. The Panel considered that it was impossible in such circumstances to determine on the balance of probabilities exactly how the guideline had been presented. No breach of Clauses 7.2 and 15.2 was thus ruled.

The Panel noted each party's submission in relation to the Acomplia data. The representative stated that he had made it clear that he was discussing the SERENADE data and not the RIO-Diabetes study. The Acomplia detail aid clearly referred to the SERENADE study. It appeared that the complainant was concerned that he in error had referred to the RIO-Diabetes study but that this error had not been corrected by the representative. It was impossible to determine on the balance of probabilities what had been said and the Panel thus ruled no breach of Clauses 7.2 and 15.2.

The Panel noted the allegation that Acomplia had been promoted outside of its marketing authorization. The Panel noted that Acomplia was licensed 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. The Panel noted that it was not unacceptable to mention the benefits which flowed from using a product for its licensed indication so long as any such discussion was placed firmly within the context of the product's licensed indication. The Panel noted that the detail aid referred to

overweight patients. The relevant representatives' briefing material began 'Identify overweight patients with type 2 diabetes as the patient group we would like to discuss'. This was not unacceptable. Again the Panel considered that it was impossible to determine on the balance of probabilities exactly what had been said and ruled no breach of Clauses 3.1, 7.2 and 15.2.

The Panel noted that according to both parties the discussion of Acomplia had included mention of glitazones. Both parties also agreed that the complainant had asked a question about this matter. However the parties' accounts differed. In addition the complainant had been absent for the beginning of the relevant discussion. According to the complainant he had returned to the meeting room during a discussion about the use of Acomplia instead of a glitazone and had sought clarification of the representative's comments. The complainant did not provide his understanding of how this discussion had started. According to Sanofi-Aventis in response to a question about Acomplia and diabetics the representative explained that local practices used Acomplia in type 2 diabetics in whom weight loss was appropriate. Thereafter, when asked if it was being used in place of other medicines the representative stated that some local practices had used Acomplia in place of a glitazone. The Panel did not accept the company's suggestion that it could rely on the exemption to the definition of promotion set out in Clause 1.2. If the company's version of the discussion was correct it did not appear that the representative had necessarily been asked about replacement of glitazone with Acomplia.

The Panel noted that representatives could respond to unsolicited questions about the unlicensed use of their products so long as the criteria set out in Clause 1.2 and its supplementary information were satisfied. Representatives should be extremely cautious when responding to such requests. It was difficult for representatives to satisfy the criterion given their role, particularly at a group promotional meeting. Attendees were likely to view the representatives' comments in the context of promotion. The safest course of action was to forward such requests to the company's medical information department.

Whilst there were some similarities the parties' accounts differed. In particular the complainant was absent at the beginning of the relevant discussion. It was not possible to determine on the balance of probabilities exactly what had been said and thus the applicability of the exemption to the definition of promotion. No breach of Clauses 15.2 and 3.1 was ruled.

Complaint received	**23 April 2007**
Case completed	**3 August 2007**

GLAXOSMITHKLINE v TAKEDA

Actos mailing

GlaxoSmithKline complained about a mailing issued by Takeda which notified GPs that Actos (pioglitazone) could now be used in combination with insulin in type 2 diabetics with insufficient glycaemic control on insulin for whom metformin was inappropriate. The mailing also referred to Competact, a fixed-dose combination of pioglitazone and metformin. GlaxoSmithKline noted that Competact was contraindicated for use in combination with insulin.

GlaxoSmithKline complained about a number of matters and referred to inter-company dialogue. It disclosed, however, that agreement had been reached on some of the matters and so these did not proceed. With regard to another three matters, Takeda acknowledged that it had had inter-company dialogue on all of them but stated that it had reached agreement on two. Nonetheless, Takeda's response to the Authority covered all three points and the Panel ruled on all three. Takeda appealed the Panel's rulings on two of the points on the basis that the companies had previously come to an agreement on them and thus they should not have been considered by the Panel.

Paragraph 5.2 of the Constitution and Procedure stated that 'A complaint from a pharmaceutical company will be accepted only if the Director is satisfied that the company concerned has previously informed the company alleged to have breached the Code that it proposed to make a formal complaint and offered inter-company dialogue at a senior level in an attempt to resolve the matter but that this offer was refused or dialogue proved unsuccessful. A formal statement detailing the actions taken must be provided'.

In relation to GlaxoSmithKline's complaint about three separate matters the Panel ruled breaches of the Code. On appeal the Appeal Board was concerned that in inter-company correspondence Takeda had responded slowly and GlaxoSmithKline had not been justified in seeking a 'written undertaking' on matters agreed by Takeda, nonetheless given that a complaint could only proceed if inter-company dialogue had not been successful, the Panel's rulings on the two points where agreement had been reached, were declared a nullity; they would no longer stand.

The only matter upon which the companies had not agreed related to Competact. GlaxoSmithKline considered that as the mailing at issue was intended to highlight the new indication for Actos ie concomitant use with insulin, then any mention of Competact should be qualified with a statement that it was contraindicated for use in combination with insulin.

GlaxoSmithKline had serious concerns about the unqualified mention of Competact in this promotional context, and alleged that this misrepresented the situation and was not in accordance with the terms of Competact's marketing authorization.

The Panel noted that the Competact summary of product characteristics (SPC) stated that it was contraindicated for use in combination with insulin. The Panel noted that a treatment algorithm in the Actos mailer outlined five distinct treatment options for type 2 diabetics, in five vertical columns. The final purple box in four of the five vertical columns read either 'Rx Actos' or 'Add Actos'. The final box in the third column was pink, rather than purple and read 'Rx Competact'. This was followed by 'Competact: Actos + metformin combination tablet'. The Panel considered that within the context of a mailing which addressed the treatment of type 2 diabetics and highlighted the fact that Actos had now been licensed to be used in combination with insulin in type 2 patients with insufficient glycaemic control on insulin, the failure to state the relevant contraindication was misleading and inconsistent with the Competact SPC. The Panel noted Takeda's submission that the reason the contraindication had not yet been removed to bring it in line with Actos was an administrative matter, however promotion had to be in accordance with the marketing authorization and not inconsistent with the SPC. Breaches of the Code were ruled.

Upon appeal by Takeda the Appeal Board noted that an arrow ran along the bottom of the algorithm from left to right marked 'Progression of Type 2 diabetes'. The first time that insulin was introduced as a treatment option was in the last box on the right hand side. The last vertical column stated in successive boxes '… on insulin', 'metformin contraindicated or not tolerated', 'WHAT NEXT?', 'Add Actos', and finally below the last box 'Actos + insulin combination therapy'.

The Appeal Board considered that the inclusion of Competact in the treatment algorithm without noting its contraindication for use in combination with insulin was not misleading, as its treatment position of type 2 diabetics in the algorithm at position three was before the introduction of insulin at position five.

The Appeal Board further noted that that Competact was a combination of pioglitazone and metformin neither of which were contraindicated with insulin. Thus the absence of the contraindication in this instance should not give rise to safety issues. The Appeal Board ruled no breaches of the Code. The appeal was successful.

GlaxoSmithKline UK Limited complained about a four page mailing (ref AC070230) for Actos (pioglitazone) issued by Takeda UK Limited which notified GPs of the addition of a new indication. GlaxoSmithKline supplied Avandia (rosiglitazone).

GlaxoSmithKline explained that the Actos marketing authorization had recently been extended with the addition of the following: 'Pioglitazone is also indicated for combination with insulin in type 2 diabetes mellitus patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance'. (Section 4.1 of the Actos summary of product characteristics (SPC)).

The mailing also referred to Competact, a fixed-dose combination of pioglitazone and metformin, which was also marketed by Takeda. In the context of the mailing at issue GlaxoSmithKline noted that the Competact SPC Section 4.2 Contraindications stated: 'Competact is also contraindicated for use in combination with insulin'.

Takeda explained that prescribing Actos in combination with insulin was likely to be initiated in secondary care rather than in primary care and hence this mailer was intended to alert GPs that they might see patients coming to them from secondary care on this combination.

GlaxoSmithKline complained about a number of matters and referred to inter-company dialogue. It disclosed, however, that agreement had been reached on some of the matters and so these did not proceed. With regard to another three matters, Takeda acknowledged that it had had inter-company dialogue on all of them but stated that it had reached agreement on two. Nonetheless, Takeda's response to the Authority covered all three points and the Panel ruled on all three. Takeda appealed the Panel's rulings on two of the points on the basis that the companies had previously come to an agreement on them and thus they should not have been considered by the Panel.

Paragraph 5.2 of the Constitution and Procedure stated that 'A complaint from a pharmaceutical company will be accepted only if the Director is satisfied that the company concerned has previously informed the company alleged to have breached the Code that it proposed to make a formal complaint and offered inter-company dialogue at a senior level in an attempt to resolve the matter but that this offer was refused or dialogue proved unsuccessful. A formal statement detailing the actions taken must be provided'.

In relation to GlaxoSmithKline's complaint about three separate matters on which the Panel ruled breaches of the Code, the Appeal Board noted that the full documentation on inter-company dialogue had not been submitted until the appeal and considered that without this new material it would have been difficult to decide what had been agreed. The Appeal Board considered that it would be helpful if the Director had been clearer in documenting the decision regarding which matters were to proceed as complaints. The Appeal Board was not reviewing the Director's decision. It was reviewing whether the Panel was correct to rule on the complaint.

The Appeal Board noted that Takeda had confirmed by email on 20 April that it agreed to: 'reflect the licence wording on all future pieces concerning the licence in combination with insulin as per the minutes' and '… to review the wording used in relation to adverse events and safety in relation to the use of Actos in combination with insulin as noted in the minutes. We will ensure that the wording used adequately reflects the new SmPC …' (points 1 and 3). Thus the only outstanding issue was Takeda's decision not to include the contraindication of Competact with insulin in the treatment algorithm on page 2 of the mailing. The Appeal Board noted that on 24 April GlaxoSmithKline had asked Takeda to confirm its confirmed actions points 1 and 3 (noted above) by written undertaking. In addition the email noted that GlaxoSmithKline would proceed to the PMCPA on point 2 as no agreement had been reached. Takeda had confirmed its email of 20 April on 2 May by email; this was the same day that GlaxoSmithKline complained to the PMCPA.

The Appeal Board was concerned about the behaviour of each company as evidenced in the inter-company dialogue. Takeda had been rather slow to respond to emails from GlaxoSmithKline. Nonetheless the Appeal Board considered that Takeda's emails of 20 April and 2 May had provided sufficient confirmation that agreement had been reached on points 1 and 3. GlaxoSmithKline had not been justified in seeking a 'written undertaking' on matters clearly agreed by Takeda. The Appeal Board noted that the Director had been correct to rule that the complaint should proceed only in relation to those points responded to by Takeda on which no agreement was reached. This meant that the complaint should have proceeded on one point only and not the other two. The Appeal Board thus declared the Panel's rulings on two of the points a nullity; they would no longer stand and are therefore not included in this report.

The Appeal Board considered that GlaxoSmithKline's decision to complain about matters upon which agreement had been reached was regretable. In the Appeal Board's view, any complaint submitted to the Authority should be absolutely clear about the status of inter-company dialogue.

COMPLAINT

GlaxoSmithKline noted that the second page of the mailing featured an algorithm for the treatment of type 2 diabetes. This included a highlighted mention of Competact, Takeda's pioglitazone/metformin combination. Competact was contraindicated with insulin. As the mailing was self-evidently intended to principally draw attention to the new pioglitazone indication for concomitant use with insulin GlaxoSmithKline's strong view was that any mention of Competact should be qualified with a comment drawing the prescriber's attention to the fact that

Competact was contraindicated for use in combination with insulin.

GlaxoSmithKline had serious concerns about the unqualified mention of Competact in this promotional context, and alleged that this misrepresented the situation and was not in accordance with the terms of Competact's marketing authorization in breach of Clauses 3.2 and 7.2 of the Code.

RESPONSE

Takeda explained that the second page of the mailing set the new indication into context with the other licensed indications for pioglitazone as there had been two recent changes to the licence (combination with insulin and triple combination therapy). As a result there were five separate indications/treatment pathways which could confuse prescribers, particularly those in primary care for whom Takeda did not have a permanent field force. (Takeda employed a very small group of regional account directors who saw a very small percentage of all GPs in addition to health professionals in primary care trusts and secondary care.)

It was clear in the algorithm that each vertical column represented a separate prescribing scenario. Hence in accordance with the licence the algorithm was set up at the top with the express caveat of 'In patients requiring additional glycaemic control ...' and this read on to each column separately. The far right column represented the new indication and it was clear from the words used and the display of the prescribing situations that this was the only part of this algorithm which related to the new licence.

In addition, Takeda also marketed Competact (pioglitazone/metformin) for use in type 2 diabetics and this was included in the algorithm to demonstrate to doctors where it fitted in the whole spectrum of treatment options available. Apart from this one mention in the algorithm, there were no claims about Competact in the mailing and the one column containing the prescribing scenario for Competact was clearly distinct from the Actos columns.

The algorithm clearly detailed the various licence options involving pioglitazone in an easy to read form so that the prescriber could readily determine the exact positioning of pioglitazone in all possible treatment settings. There was no mention of insulin in the section relating to the use of Competact. The Competact section read: 'In patients requiring additional glycaemic control ... on maximum tolerated dose of metformin …. Preference for minimum tablets …. What next? ... prescribe Competact'. In addition the contraindication with insulin was stated in the Competact prescribing information on page 4. In addition neither of the components of Competact (Actos and metformin) was contraindicated for use in combination with insulin. As such there was no implication for patient safety.

The fact that the contraindication for Competact had not yet been removed to bring it in line with Actos was an administrative matter, in that the submission for this change could only be made after the licence change was approved for Actos. Apart from this one mention in the algorithm, there were no claims made concerning Competact in the mailing and hence Takeda did not consider it necessary to make any additional qualification as the prescribing information for Competact was on the back page of the mailing.

PANEL RULING

The Panel noted that Section 4.3 of the Competact SPC stated that it was contraindicated for use in combination with insulin. The Panel noted that the Actos treatment algorithm outlined five distinct treatment options for type 2 diabetics, in five vertical columns. The final purple box in four of the five vertical columns read either 'Rx Actos' or 'Add Actos'. The final box in the third column was pink, rather than purple and read 'Rx Competact'. This was followed by 'Competact: Actos + metformin combination tablet'. The Panel considered that within the context of a mailing which addressed the treatment of type 2 diabetics and was designed to highlight a change in the licence whereby Actos had now been licensed to be used in combination with insulin in type 2 patients with insufficient glycaemic control on insulin, the failure to state the relevant contraindication was misleading and inconsistent with the Competact SPC. The Panel noted Takeda's submission that the reason the contraindication had not yet been removed to bring it in line with Actos was an administrative matter, however promotion had to be in accordance with the marketing authorization and not inconsistent with the SPC. Breaches of Clauses 3.2 and 7.2 were ruled.

APPEAL BY TAKEDA

Takeda submitted that the aim of the mailing was to tell primary care health professionals that, due to a recent licence extension, Actos could now be used in combination with insulin. This specific aim was made very clear, and was consistently referred to throughout the document.

Takeda submitted that UK clinical practice was such, that apart from GPs with a special interest, primary care health professionals were not routinely involved in the active management of insulin treatment in patients with type 2 diabetes. Therefore it was important that widespread notification, in the form of the mailer, was sent to all the generalist primary care physicians in the UK so as to avoid any confusion in the use of Actos with insulin, which until recently had been contraindicated. Takeda submitted that the change from a specific contraindication to an indication was really quite rare in regulatory terms and could potentially cause major confusion in primary care; patients could be taken off therapies which had been initiated in secondary care to the detriment of their glycaemic control.

Promotional information was, however, sent to secondary care health professionals including GPs with a special interest in diabetes, by means of a

mailer which focussed solely on the new indication for Actos and which included the clinical data on which this licence change was based.

Takeda submitted that given the recent, numerous licence changes for Actos, the mailer was designed to place in context all of the available treatment options for pioglitazone, so as to give the physician a more simplified overview to help them make the appropriate prescribing choices. As Competact was a relatively new available fixed-dose combination of pioglitazone/metformin, the treatment algorithm as shown on page 2 would be incomplete if some reference to it were not included. This was the only time that Competact was mentioned in the mailer, which clearly was not designed to specifically promote it and for which other mailers had been used to undertake this role. At no point did the mailer allude to any change in the licence for Competact.

Takeda submitted that in terms of its purpose being one of notification the mailer was quite clear as to its intent as follows: 'Actos. The ONLY glitazone with a licensed indication for use in combination with insulin'; 'What does this licence change mean for you and your patients?' and 'Actos; Helping insulin to reduce HbA_{1C}'.

Takeda submitted that the claims were all related to Actos, with no mention of Competact, and the licence change was referred to in the singular rather than the plural. Finally, the Actos logo was at the bottom of the page and the mailer was in the Actos brand colours, not the Competact ones.

Takeda submitted that the third page of the mailer clearly set out the context for the new licensed indication for Actos, as it stated 'This newly licensed indication provides diabetes specialists with a strong rationale to prescribe Actos in combination with insulin when metformin is contraindicated or not tolerated', 'Consequently you may see patients who are treated in secondary care receiving Actos + insulin therapy'. Once again the reference to the licence change was purely related to Actos, not to Competact, and the page was in the Actos brand colours with the Actos brand logo.

Takeda submitted that the treatment algorithm had been included to clarify the therapeutic indications as written in Section 4.1 of the Actos and, for the reason stated above, Competact SPCs. It was for this reason alone that Competact prescribing information had been included. Indeed if this was even considered to be an abbreviated advertisement for Competact, then in accordance with Clause 5 of the Code, the contraindications for use would not need to be specifically stated. In clinical practice it was acknowledged that treatment algorithms gave the indication for use of a particular product or therapy rather than their contraindications for use, and this format was followed on page 2.

Takeda submitted that the new licensed indication for Actos was, in any case, very different to the sole and unchanged licensed indication for Competact. This was clearly indicated in the treatment algorithm; for the new licensed indication it was stated that: 'Actos can only be given to Type 2 diabetes patients who are already on insulin, and for whom metformin is contraindicated or not tolerated'. This was quite different to the licence for Competact which stated 'Competact can only be given as a form of dual oral therapy to patients who are on the maximum tolerated dose of metformin'.

Takeda submitted that thus there was no scope for confusion between the two licensed indications as patients on insulin, requiring further glycaemic control, could only be given Actos (not Competact) for, as the treatment algorithm clearly showed metformin (one of the components of Competact) must be contraindicated or not tolerated in this situation. Similarly for the Competact arm of the algorithm there was no mention of a progression in treatment to include insulin.

COMMENTS FROM GLAXOSMITHKLINE

GlaxoSmithKline disagreed that, apart from GPs with a special interest in diabetes, primary care health professionals were not routinely involved in the active management of insulin treatment in type 2 diabetics. Diabetes formed part of the Government's Quality and Outcome Framework targets and so many GPs would be involved in the active management of these patients to ensure target HbA_{1C} levels were met. GlaxoSmithKline noted that one university ran a course specifically to train such health professionals. Non-specialist GPs would review patients on insulin and consider whether to add pioglitazone to those with insufficient glycaemic control (when metformin was inappropriate because of contraindications or intolerance).

Takeda stated that the change from a specific contraindication to an indication had the potential to cause confusion in primary care. Following on from this argument, GlaxoSmithKline strongly believed that the promotion of a new indication for Actos for which Competact was contraindicated in an item where both products were mentioned, had the ability to confuse and mislead if the contraindication with insulin for Competact was not mentioned. Health professionals might believe that Competact also had a licence with insulin, leading to prescribing that might jeopardise patient safety.

GlaxoSmithKline noted that the piece was clearly entitled as an Actos promotional leaflet in combination with insulin. GlaxoSmithKline alleged that by including Competact within the leaflet without clarity regarding the specific contraindication was misleading. As such GlaxoSmithKline agreed with the Panel's ruling in this regard and found Takeda's insistence that this was an Actos piece further reinforcement regarding the inappropriate inclusion of Competact.

GlaxoSmithKline alleged that the algorithm had a clear arrow indicating progression of type 2 diabetes, which one would then assume for treatment

progression with addition of multiple agents. It would be common clinical practice for prescribers to change patients from Actos to Competact then add in additional therapies when required, such as insulin, however there was no clarification or indication to a prescriber that this combination was contraindicated. GlaxoSmithKline additionally disagreed that the flow chart on page 2 was a genuine treatment algorithm. A treatment algorithm would refer to a wide range of products and be referenced to guidelines. As a free standing piece this could not be considered to be an abbreviated advertisement. As such GlaxoSmithKline alleged that Takeda's arguments in this regard were not relevant as each piece had to stand on its own merits and not those of a hypothetical piece of abbreviated advertising.

APPEAL BOARD RULING

The Appeal Board noted that the Actos treatment algorithm outlined five distinct treatment options for type 2 diabetics, in five vertical columns. The final box in the third column was pink, rather than purple and read 'Rx Competact'. This was followed by 'Competact: Actos + metformin combination tablet'. The Appeal Board noted that an arrow ran along the bottom of the algorithm from left to right marked 'Progression of Type 2 diabetes'. The first time that insulin was introduced as a treatment option was in the last box on the right hand side. The last vertical column stated in successive boxes '… on insulin', 'metformin contraindicated or not tolerated', 'WHAT NEXT?', 'Add Actos', and finally below the last box 'Actos + insulin combination therapy'.

The Appeal Board considered that the inclusion of Competact in the treatment algorithm without noting its contraindication for use in combination with insulin was not misleading, as its treatment position of type 2 diabetics in the algorithm at position three was before the introduction of insulin at position five.

The Appeal Board further noted that that Competact was a combination of pioglitazone and metformin neither of which were contraindicated with insulin. Thus the absence of the contraindication in this instance should not give rise to safety issues.

The Appeal Board noted that although the mailing addressed the treatment of type 2 diabetics and was designed to highlight a change whereby Actos was now licensed to be used in combination with insulin in type 2 patients with insufficient glycaemic control on insulin for whom metformin was contraindicated or not tolerated, the failure to state the relevant contraindication for Competact was not misleading. The Appeal Board ruled no breach of Clauses 3.2 and 7.2. The appeal on this point was successful.

Complaint received	**8 May 2007**
Case completed	**4 October 2007**

CASE AUTH/2006/5/07

PHARMACIST PRACTITIONER v GLAXOSMITHKLINE

Promotion of Seretide

A pharmacist practitioner at a general practice complained about the promotion of Seretide (salmeterol/fluticasone) by GlaxoSmithKline.

Seretide was indicated for the symptomatic treatment of patients with severe chronic obstructive pulmonary disease (COPD) (FEV1 <50% predicted normal) and a history of repeated exacerbations, who had significant symptoms despite regular bronchodilator therapy.

The complainant was at a GlaxoSmithKline meeting where the representatives had displayed a graph, apparently from the Towards a Revolution in COPD Health (TORCH) study showing the mortality outcome. This was annotated in large type highlighting the 16% reduction in mortality, which was not statistically significant. Text below was along the lines of 'Seretide led to a non-statistically significant 16% reduction in mortality'. The complainant's concern was that although factual the graph was unprofessional and misleading, to a passing observer, to which it was targeted, it could be construed as stating Seretide reduced mortality in COPD, which it did not. The outcome was not statistically significant.

The Panel noted that the exhibition display comprised three panels. That described by the complainant was headed 'TORCH 3 YEAR Landmark Study' followed by 'Primary outcome - Seretide 500 Accuhaler survival result'. A graph beneath plotted the probability of death (%) against time to death (years) alongside an emboldened downward arrow and the prominent claim '16.5% risk reduction with Seretide 500 Accuhaler vs control p=0.096'. A highlighted box underneath read 'TORCH shows a trend towards improved survival with Seretide 500 Accuhaler vs control over 3 years which is non-statistically significant - the probability of death at any point over the 3 year study was reduced by 16.5% with Seretide 500 Accuhaler vs control (p=0.096)'.

The Panel considered that overall the exhibition panel detailing the mortality data did not make it sufficiently clear that the data was not statistically significant, particularly given the description of TORCH as a landmark study. The Panel considered that on glancing at the exhibition panel delegates would be struck by the prominent subheading 'Primary outcome - Seretide 500 Accuhaler survival result'. The results were then depicted in the graph which showed a visual difference between Seretide and the control group alongside the emboldened arrow and '16.5%' which was in a larger, bolder typeface than the explanatory text immediately below. A delegate who did not take the time to read the entire exhibition panel would be left with the impression that the 16.5% risk reduction was statistically significant. The Panel considered that graph was misleading and that its content could not be qualified by the text below. Breaches of the Code were ruled.

A pharmacist practitioner at a general practice, complained about the promotion of Seretide (salmeterol/fluticasone) by GlaxoSmithKline UK Ltd.

Seretide was indicated for the symptomatic treatment of patients with severe chronic obstructive pulmonary disease (COPD) (FEV1 <50% predicted normal) and a history of repeated exacerbations, who had significant symptoms despite regular bronchodilator therapy.

COMPLAINT

The complainant explained that he had attended a GlaxoSmithKline meeting where the representatives had had a number of small display boards. The first of these pictured a graph, apparently from the Towards a Revolution in COPD Health (TORCH) study showing the mortality outcome in the study. This was annotated in large type highlighting the 16% reduction in mortality, which was not statistically significant. Text below reinforced the 16% reduction, the complainant could not remember the exact wording but it was along the lines of 'Seretide led to a non-statistically significant 16% reduction in mortality'.

The complainant was concerned that, although factual, the use of such material was unprofessional and misleading. To a passing observer, to which these boards were targeted, they could be construed as stating Seretide reduced mortality in COPD, which it did not. Since the outcome was not statistically significant the complainant saw no place for promoting it or stating other than there was no effect seen.

When writing to GlaxoSmithKline, the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

GlaxoSmithKline noted that the exhibition panel in question was entitled 'Primary Outcome – Seretide 500 Accuhaler survival result' (measured as all-cause mortality). The graph on the exhibition panel plotted the probability of death (%) vs time to death (years) and clearly reflected the non-significant 16.5% risk reduction seen with Seretide Accuhaler vs control. As the TORCH study included a patient group some of whom fell outside the licensed indication for Seretide in COPD, this relative risk reduction represented the sub-group analysis which only included patients within the UK licence for Seretide (FEV1 < 50%). The

p-value [p=0.096] was clearly shown on the graph and also stated in the associated text. It was also made clear that the primary endpoint did not reach statistical significance so as not to mislead. In the TORCH paper the authors suggested that the lower than anticipated number of deaths and the high withdrawal rate in patients receiving placebo (who were free to receive active therapy subsequently, including Seretide), might have contributed to the final results not reaching statistical significance.

As mentioned above, the mortality data represented the primary outcome of this landmark study. GlaxoSmithKline noted that it also presented a secondary endpoint [quality of life] from the study in another exhibition panel displayed at the meeting. To be able to present the secondary endpoint of this study it was important to clearly inform health professionals that the primary endpoint was statistically not significant to enable all the available evidence from the study to be put in context in a transparent manner. GlaxoSmithKline had not made any mortality claims. The need to present study data in the context of its primary parameter had been considered in a previous case (AUTH/1579/4/04) which GlaxoSmithKline took into consideration in preparing these materials to ensure balance and so as not to mislead.

The TORCH study was the first and largest study to prospectively investigate the potential for medicines to impact survival in patients with COPD and had been considered a landmark COPD study. It would be misleading, unprofessional and unethical to talk to health professionals about a clinically important study without reporting the primary endpoint or saying 'no effect seen' as suggested. Even though the primary endpoint was statistically not significant it was of clinical interest given the landmark nature of the study.

GlaxoSmithKline disagreed with the complainant's submission that the exhibition panel was 'targeted at' a 'passing observer'. It was exhibited at a meeting for health professionals capable of interpreting the relative importance of this data; if they had any questions they could have discussed these with a representative on the stand.

GlaxoSmithKline believed that the material presented in the exhibition panel was accurate, balanced, objective and unambiguous and based on an up-to-date evaluation of the evidence. It was clearly substantiated and the finding of a statistically non-significant primary endpoint was prominently stated. Therefore GlaxoSmithKline firmly believed that the exhibition panel reflected the TORCH primary outcome result and was thus not in breach of either Clause 7.2 or Clause 7.4.

PANEL RULING

The Panel noted that the exhibition display comprised three panels. That described by the complainant was headed 'TORCH 3 YEAR Landmark Study' followed by 'Primary outcome - Seretide 500 Accuhaler survival result'. A graph beneath plotted the probability of death (%) against time to death (years) alongside an emboldened downward arrow and the prominent claim '16.5% risk reduction with Seretide 500 Accuhaler vs control p=0.096'. A highlighted box underneath read 'TORCH shows a trend towards improved survival with Seretide 500 Accuhaler vs control over 3 years which is non-statistically significant - the probability of death at any point over the 3 year study was reduced by 16.5% with Seretide 500 Accuhaler vs control (p=0.096)'. One accompanying exhibition panel featured a photograph of a man and a boy and the claim 'Seretide is for patients who still have so much to live for'. The third presented the 3 year quality of life data, a secondary outcome wherein Seretide patients demonstrated a 2.7 improvement in their adjusted mean 3 year quality of life score vs a 0.7 decline in the control group; p<0.001.

The Panel noted GlaxoSmithKline's explanation that to be able to present the secondary endpoint data it was important to tell health professionals that the primary endpoint was not statistically significant. The Panel noted that nonetheless each exhibition panel had to be capable of standing alone as regards the requirements of the Code. The Panel considered that overall the exhibition panel detailing the mortality data did not make it sufficiently clear that the data was not statistically significant particularly given the description of TORCH as a landmark study. The Panel considered that on glancing at the exhibition panel delegates would be struck by the prominent subheading 'Primary outcome - Seretide 500 Accuhaler survival result'. The results were then depicted in the graph which showed a visual difference between Seretide and the control group alongside the emboldened arrow and '16.5%' which was in a larger, bolder typeface than the explanatory text immediately below. A delegate who did not take the time to read the entire exhibition panel would be left with the impression that the 16.5% risk reduction was statistically significant. The Panel considered that graph was misleading and that its content could not be qualified by the text below. This initial impression of the exhibition panel was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

Complaint received **30 May 2007**

Case completed **26 July 2007**

ANONYMOUS v FLYNN PHARMA

Promotion of Medikinet

An anonymous complainant stated that he had received some inappropriate mailings from Flynn Pharma regarding Medikinet, a product for attention deficit hyperactivity disorder (ADHD). The complainant did not and had never treated ADHD. He had also received a reply paid card (RPC) and a representative had telephoned him requesting an appointment. It did not state on the RPC anything about having to grant a representative an appointment. A colleague had been given a drug and therapeutics committee application form by a representative; the complainant understood that these should not be handed out by representatives. The colleague was also provided with a clinical paper in German, and was told that there was no English translation.

The complainant had also been invited to a meeting and considered this was inappropriate as he did not treat ADHD. The complainant requested that the company be more specific with its targeting.

The Panel noted that the Code required promotional material to be sent or distributed to those people whose need for, or interest in, the particular information could reasonably be assumed; it should be tailored to the audience to whom it was directed. Medikinet XL treatment had to be supervised by a specialist in childhood behavioural disorders. The introductory mailing was sent to doctors whose names were on a commercial database of child psychiatrists and paediatricians. The Panel considered that although the first group were likely to initiate treatment, general paediatricians were likely to be responsible for maintaining treatment under the supervision of such a specialist. In the Panel's view, although the mailing was mainly aimed at the primary prescriber the distribution of the mailing was not unreasonable. Both psychiatrists and paediatricians would become involved in treatment. It was not in the interests of a company to promote a product other than to those who would need to be familiar with it. No breach of the Code was ruled.

The Panel noted that it knew neither the identity nor the professional status of the complainant. The complainant had stated that (s)he did not and had never treated ADHD. The Panel did not know, however, if the complainant was such that (s)he might reasonably be assumed to be responsible for some patients with ADHD who stayed under the supervision of a specialist. The Panel did not think it was unreasonable for a representative to seek an appointment with such individuals; such requests should comply with the Code. The complainant had provided a copy of a completed RPC from which it appeared that (s)he had requested a memory stick and reprints of key papers. There was no evidence that the representative had subsequently attempted to use the materials as an inducement to gain an interview. The complainant was anonymous and had provided no contact details and so it was impossible to seek further information from him/her, or from the representative, about what was said during the telephone call. There was no evidence that the representative had repeatedly tried to see the complainant or that any inducement or subterfuge had been employed. No breach of the Code was ruled.

The complainant referred to a drug and therapeutics application form provided to a colleague by a representative. This application form gave a detailed profile of Medikinet. The company stated that this form was normally provided on request. No information about the circumstances of its provision was provided by the complainant. No breach of the Code was accordingly ruled.

The Panel noted Flynn's explanation that as the drug and therapeutic application form cited a paper published in German the original reference was included to substantiate the point made. In the Panel's view this was not helpful and an English translation should have been provided. There was no information about whether the complainant's colleague had requested substantiation for a claim etc. It appeared from Flynn's submission that the German reference was always supplied with the drug and therapeutics document. The Panel did not consider there had been a breach of the Code in this regard. If a request for substantiation had been made then the company would have had to supply substantiation in English.

An anonymous complainant complained about material he and his colleagues had received from Flynn Pharma Ltd about Medikinet (controlled release methylphenidate) and telephone calls made by one of the company's representatives. Copies of a mailing which included a reply paid card (RPC) and a document entitled 'New Medicines Profile D&T Application – Medikinet XL' were provided together with a clinical paper published in German, Döpfner *et al*.

COMPLAINT

The complainant explained that he had recently received some inappropriate mailings from Flynn Pharma regarding Medikinet, a product for attention deficit hyperactivity disorder (ADHD). The complainant did not and had never treated ADHD. He also received an RPC and a representative had

telephoned him requesting an appointment. It did not state on the RPC anything about having to grant a representative an appointment. This had also happened to a colleague who had also been given a drug and therapeutics committee application form from a representative. He understood that this was considered a piece of medical information and should not be handed out by representatives. The complainant's colleague had also been given a clinical paper in German, and was told that there was no English translation. The complainant was unsure how this stood with the Code, but observed that it was of no use whatsoever.

The complainant had also been invited to a meeting on 4 June. Again this was totally inappropriate as he did not treat ADHD.

The complainant requested that the company be more specific with its targeting as this was becoming a hassle and a waste of his time.

Flynn was asked to respond to Clauses 12.1 and 15.3 of the Code.

RESPONSE

Flynn explained that Medikinet XL was launched in the UK in March 2007. An introductory mailing was sent to child psychiatrists and paediatricians, these being the prescribing groups that might initiate and manage treatment of ADHD. Flynn noted that Clause 12.1 required promotional material only to be sent to those categories of persons whose need for, or interest in, the particular information could be reasonably assumed (emphasis added). Doctors' names were taken from a commercial database of such professionals. Unfortunately there was no precise way of targeting health professionals, particularly those within a sub-speciality, but the company considered its approach to be sensible and reasonable. It would, of course, remove any health professionals from such mailing lists if it knew this was not a relevant interest area, or upon their request. An RPC attached to the mailing stated 'Please complete the reply-paid card if you would like to receive this valuable source of information' (ie further information on Medikinet XL provided on a memory stick). There was no requirement to complete or return the RPC. It was unclear from the complaint whether the complainant had done so, but a returned RPC would have indicated interest. Equally, the company hoped that a health professional who was targeted in an area outside their professional interest would not return the RPC and/or advise the company that they were not a relevant contact.

In relation to Clause 15.3 the company submitted that it did not believe the complainant had made any assertions that this was the case and respectfully submitted that there was no case to answer. The company categorically stated that, with regard to its promotional activities, there was no instruction to provide any inducements to grant or attend a meeting, prescribe a particular product or take any action in regard to Flynn, its products, services or employees.

Flynn explained that the drug and therapeutics document referred to certain data published in German and consistent with good practice, the original reference was included to substantiate the particular point made. Flynn's policy was that these were normally only issued on request. It was not, to Flynn's knowledge, an issue per se, that representatives passed or communicated medical information, which was one of the points raised by the complainant.

The complainant did not describe the circumstances leading up to the provision of the drug and therapeutics paper, but as previously stated, such items were normally provided upon request. Also Flynn did not consider it improper or inconsistent with the Code for a representative to issue 'medical information' materials. Indeed Flynn thought a situation where a representative did not or could not, would more readily provide grounds for complaint.

Given the anonymity of the complainant, the company was unable to remove their name from a contact or mailing list, but would be happy to do so. It was not in the company's interests to contact health professionals outside the field of interest and it had no wish to cause unnecessary inconvenience through such contact. Flynn had already discussed the case in general terms with the representatives to remind them of the need to ensure targeted doctors and health professionals were relevant and working within ADHD. This was simply good professional business sense.

In summary, Flynn respectfully submitted there was no case to answer with regard to a breach of the Code. This did not detract however from the fact that a health professional had complained to the Authority. Flynn apologised to the complainant for the inconvenience caused; if (s)he disclosed their identity, then the company would remove their name from its contacts database.

PANEL RULING

The Panel noted that Clause 12.1 and its supplementary information required promotional material to be sent or distributed to those categories of persons whose need for, or interest in, the particular information could reasonably be assumed. Promotional material should be tailored to the audience to whom it was directed. The Panel noted from the drug and therapeutics application form that Medikinet XL treatment had to be supervised by a specialist in childhood behavioural disorders. The introductory mailing was sent to doctors whose names were on a commercial database of child psychiatrists and paediatricians. The Panel considered that although the first group were likely to initiate treatment, general paediatricians were likely to be responsible for maintaining treatment under the supervision of such a specialist. In the Panel's view, however, the mailing at issue was mainly aimed at the primary prescriber – it was an introductory mailing. Nonetheless, the Panel did not consider that the distribution of the mailing was unreasonable. It had been sent to child psychiatrists and paediatricians – classes of health professionals who would become involved in

treatment. It was not in the interests of a company to promote a product other than to those who would need to be familiar with it. No breach of Clause 12.1 was ruled.

The Panel noted that it knew neither the identity nor the professional status of the complainant. The complainant had stated that (s)he did not and had never treated ADHD. The Panel did not know, however, if the complainant was such that (s)he might reasonably be assumed to be responsible for some patients with ADHD who stayed under the supervision of a specialist. Any material directed at such groups of people must be tailored to their needs. The Panel did not think it was unreasonable for a representative to seek an appointment with such individuals. Any such requests should comply with the Code. The complainant had provided a copy of a completed RPC from which it appeared that (s)he had requested a memory stick and reprints of key papers. There was no evidence that the representative had subsequently attempted to use the materials as an inducement to gain an interview. The complainant was anonymous and had provided no contact details and thus it was not possible to seek further information from him/her, or from the representative, about what was said during the telephone call. There was no evidence that the representative had repeatedly tried to see the complainant nor that any inducement or subterfuge had been employed. No breach of Clause 15.3 was ruled.

The complainant referred to a drug and therapeutics application form provided to a colleague by a representative. This application form detailed Medikinet, its formulation, indications, formulary implications, dose/administration, efficacy, safety, treatment alternatives including cost and its place in therapy. The company stated that this form was normally provided on request. No information about the circumstances of its provision was provided by the complainant. The company had been asked only to respond to Clauses 12.1 and 15.3. No breach of these clauses was accordingly ruled.

The Panel noted Flynn's explanation that as the drug and therapeutic application form cited a paper published in German the original reference was included to substantiate the point made. In the Panel's view this was not helpful and an English translation should have been provided. There was no information about whether the complainant's colleague had requested substantiation for a claim etc. It appeared from Flynn's submission that the German reference was always supplied with the drug and therapeutics document. The Panel did not consider there had been a breach of the Code in this regard. If a request for substantiation of a claim etc had been made then Clause 7.5 would apply and the company would have had to supply substantiation in English. The Panel asked that Flynn be advised of its concerns in this regard.

Complaint received	**7 June 2007**
Case completed	**4 July 2007**

GENERAL PRACTITIONER v SANOFI-AVENTIS

Promotion of Acomplia

A general practitioner complained about the promotion of Acomplia (rimonabant) by Sanofi-Aventis.

The complainant noted, subsequent to a ruling of no breach of the Code in Case AUTH/1976/3/07 which he did not appeal, a review of Acomplia published in the Drug and Therapeutics Bulletin, June 2007, reported that additional beneficial effects on 'Cardiometabolic Risk Factors' beyond those expected from weight loss in trials of Acomplia might not be due to the medicine itself. The complainant submitted that the article supported his original concerns about the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone'. Given the credibility of the Drug and Therapeutics Bulletin, the complainant requested that the relevance of this unproven claim for Acomplia be reconsidered.

The matter was considered as a new complaint in accordance with Paragraph 5.1 of the Constitution and Procedure. The Panel noted that the Acomplia summary of product characteristics (SPC) (Section 5.1, Pharmacodynamic Properties) stated that 'It is estimated that approximately half of the observed improvement in the HDL-C and triglycerides in patients who receive rimonabant 20mg was beyond that expected from weight loss alone'.

The review in the Drug and Therapeutics Bulletin noted that although three trial reports had stated that the effects of Acomplia on HDL-C, triglycerides and HbA_{1C} were partly independent of weight loss, it was not proven that any independent effect was wholly or partially attributable to Acomplia. The Panel noted that although the authors were not convinced about the supporting data they did not present any new evidence to refute the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors [HbA_{1C}, HDL-C and triglycerides] are beyond those expected from weight loss alone'. Given the content of the SPC and qualification contained in the claim ('An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' (emphasis added) the Panel considered that the claim was a fair reflection of the known data and could be substantiated. No breach of the Code was ruled.

A general practitioner complained about the promotion of Acomplia (rimonabant) by Sanofi-Aventis. The complainant was particularly concerned about the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone'. The claim had been most recently considered in Case AUTH/1976/3/07 where the Panel ruled no breach of the Code.

COMPLAINT

The complainant noted, subsequent to the no breach ruling in Case AUTH/1976/3/07 which he did not appeal, a review of Acomplia had been published in the Drug and Therapeutics Bulletin, June 2007. The review reported that additional beneficial effects on 'Cardiometabolic Risk Factors' beyond those expected from weight loss in trials of Acomplia might not be due to the medicine itself. The complainant submitted that the article supported his original concerns about the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone'.

Given the credibility of the Drug and Therapeutics Bulletin, the complainant invited the Panel to reconsider its ruling with regard to the relevance of this unproven effect of Acomplia in promotional materials.

The matter was considered as a new complaint in accordance with Paragraph 5.1 of the Constitution and Procedure.

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

RESPONSE

Sanofi-Aventis noted that the complainant had previously asked whether the claim that approximately 50% of Acomplia's effects on specific risk factors were beyond those expected from weight loss alone. Sanofi-Aventis had stated that the claim was based upon statements to the same effect made in the summary of product characteristics (SPC), as a result of evidence that had been demonstrated in several randomised, controlled trials that had supported the registration of Acomplia in Europe. (Copies of these were provided with the relevant sections highlighted). The complainant now questioned whether the report in the Drug and Therapeutics Bulletin negated this evidence.

Sanofi-Aventis noted that the article in the Drug and Therapeutics Bulletin was simply a review of the existing evidence qualified by the opinion of the authors. No new research had been conducted to call into question the validity of this observation, and the suggestion [in the article] that it might be based on the lifestyle advice given to participants appeared to be most unlikely given that this was applied equally to treatment and control arms. The article was simply

a review of the available evidence with this comment on the weight independent effect being only the opinion of the authors as opposed to new research or factual information to suggest that the existing knowledge of the product was incorrect. If the importance of this evidence was to be ranked, the significance of several well designed, randomised controlled trials (level 1b) would far outweigh that of expert opinion (level 4).

In summary, the Drug and Therapeutics Bulletin did not contain any new factual information to update the existing knowledge base for Acomplia, and no new data had arisen since the Panel last considered the advertisement to be consistent with the requirements of the Code. Sanofi-Aventis considered that the advertisement complied with the Code as concluded in Case AUTH/1976/3/07.

PANEL RULING

The Panel noted that the promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its SPC. The Acomplia SPC (Section 5.1, Pharmacodynamic Properties) stated that 'It is estimated that approximately half of the observed improvement in the HDL-C and triglycerides in patients who receive rimonabant 20mg was beyond that expected from weight loss alone'.

In addition to being in accordance with the terms of its marketing authorization and not inconsistent with the particulars listed in the SPC, claims for a medicine must be, *inter alia*, based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. The review in the Drug and Therapeutics Bulletin noted that although three trial reports had stated that the effect of Acomplia on HDL-C, triglycerides and HbA_{1C} was partly independent of weight loss, it was not proven that any independent effect was wholly or partially attributable to Acomplia. The Panel noted that although the authors were not convinced about the supporting data they did not present any new evidence to refute the claim 'An estimated 50% of the effects of Acomplia on Cardiometabolic Risk Factors [HbA_{1C}, HDL-C and triglycerides] are beyond those expected from weight loss alone'. Given the content of the SPC and the qualification contained in the claim 'An *estimated* 50% of the effects of Acomplia on Cardiometabolic Risk Factors are beyond those expected from weight loss alone' (emphasis added), the Panel considered that the claim was a fair reflection of the known data and could be substantiated. No breach of Clauses 7.2 and 7.4 was ruled.

Complaint received	**11 June 2007**
Case completed	**2 August 2007**

PRIMARY CARE TRUST CHIEF PHARMACIST v TAKEDA

Promotion of Actos and Competact

The chief pharmacist to a primary care trust complained about a promotional 'Dear Healthcare Professional' letter sent by Takeda which was headed with the Competact (pioglitazone/metformin) and Actos (pioglitazone) logos and entitled 'Pioglitazone – An oral anti-hyperglycaemic agent: Summary of beneficial effects on cardiovascular risk and cardiovascular outcomes in Type 2 diabetes'. The letter detailed some of the results from the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study (Dormandy *et al* 2005).

The complainant alleged that it was inappropriate to link the study results with cardiovascular benefits as the primary outcome of the PROactive study did not reach statistical significance. The use of secondary endpoints in a negative study had been criticised (Freemantle 2005).

The complainant further alleged that it was misleading to quote adverse effects from a re-analysis of the data rather than the results as originally published which showed increases in heart failure, hospitalisation from heart failure and death from heart failure.

The complainant stated that patients in the PROactive study did not have their cardiovascular medicines optimised – only 40% were on statins. In the group which was on statins, Actos failed to show an advantage.

The Panel noted that at the outset the letter informed readers that the primary endpoint, of the PROactive study, the risk of a composite cardiac outcome, had not reached statistical significance although there was a trend in favour of pioglitazone v placebo. In that regard the Panel did not consider that the PROactive study was a 'negative' study as implied by the complainant. A benefit had been shown for pioglitazone, albeit one that was not statistically significant.

Having explained the primary outcome the letter informed readers that pioglitazone significantly reduced the relative risk of the pre-defined main secondary endpoint, all-cause mortality, MI or stroke. The Panel considered that as the primary endpoint showed a trend in favour of pioglitazone, and the statistical significance of that endpoint had been explained at the outset, it was not misleading to give details of the secondary endpoint. The Panel did not consider the letter was misleading in that regard. No breach of the Code was ruled.

The letter stated 'While the incidence of serious heart failure was higher for pioglitazone-treated vs placebo-treated patients (5.7% vs 4.1%), there was no increase in the incidence of death subsequent to a report of serious heart failure (1.5% vs 1.4%, respectively)'. The Panel noted Takeda's submission that these figures were from the primary analysis of the PROactive study and not from a re-analysis as alleged. The Panel noted the author's comment 'Consistent with the reported side-effect profile for pioglitazone, there was an increased rate of oedema and heart failure, though mortality due to heart failure did not differ between groups'. The Panel considered that the statement in the letter about heart failure was not misleading as alleged and could be substantiated. No breaches of the Code were ruled.

The Panel noted the complainant's concern that only 40% of patients in the PROactive study were on statins and in that regard their cardiovascular therapy was not optimal. Dormandy *et al* noted that study investigators were, however, required, throughout the study, to increase all therapy to an optimum according to the international guidelines. Particular attention was drawn to the need to, *inter alia*, optimise lipid-altering therapy. In that regard the Panel did not consider that patients had not been optimally treated as alleged. The Panel also noted Takeda's submission that statistical analysis showed that baseline, statin-use or non-use, did not predict beneficial response to pioglitazone. This did not support the complainant's statement that, in the groups that were on statins, Actos failed to show an advantage. The Panel did not consider that the letter at issue was misleading in this regard. No breach of the Code was ruled.

The chief pharmacist to a primary care trust complained about a promotional 'Dear Healthcare Professional' letter (ref AC070548) sent by Takeda UK Limited. The letter was headed with the Competact (pioglitazone/metformin) and Actos (pioglitazone) logos and entitled 'Pioglitazone – An oral anti-hyperglycaemic agent: Summary of beneficial effects on cardiovascular risk and cardiovascular outcomes in Type 2 diabetes'. The letter detailed some of the results from the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study.

COMPLAINT

The complainant noted that the letter described the PROactive study and linked the study results with cardiovascular benefits. However the complainant alleged this was inappropriate as the primary outcome of the study did not reach statistical significance. The complainant noted that the use of secondary endpoints

in a negative study had been criticised (Freemantle 2005).

The complainant further alleged that it was misleading to quote adverse effects from a re-analysis of the data rather than the results as originally published which showed increases in heart failure, hospitalisation from heart failure and death from heart failure.

The complainant stated that patients in the PROactive study did not have their cardiovascular medicines optimised – only 40% were on statins. In the group which was on statins, Actos failed to show an advantage.

The Authority asked Takeda to respond to the requirements of Clauses 7.2, 7.4, 9.1 and 9.2 of the Code.

RESPONSE

Takeda explained that the letter in question was generated in response to the number of enquiries about the beneficial effects of Actos on cardiovascular risk factors and outcomes and was designed to give health professionals the recent, updated, assessment of these effects as determined by the European Medicines Evaluation Agency (EMEA) and incorporated into the new, revised, European Public Assessment Record (EPAR). In addition, it was designed to draw attention to some recent publications from the PROactive clinical trial, which had appeared in international, peer-reviewed journals, and so allow health professionals to gain further information on this important area.

The letter summarised in an accurate, balanced, fair, and objective manner, some, (but not all) of the beneficial cardiovascular effects and outcomes which had been seen with the Actos in the PROactive study (Dormandy *et al*, 2005) whilst also referring to the cardiovascular adverse effects, ie oedema and heart failure which were acknowledged side effects of Actos, so as to enable health professionals to form their own opinion as to the therapeutic value of using Actos in type 2 diabetics with macrovascular disease.

The letter was posted at the beginning of June, since when the company had received very positive feedback from health professionals who considered it was factual, clear and concise and gave a good overview of both the benefits and the risks. Consequently the company was surprised to receive this one complaint.

Takeda stated that several of the complainant's comments about the PROactive study were either incorrect or at odds with international medical and scientific opinion as given by EMEA, the European Association of the Study of Diabetology (EASD), the PROactive Steering Committee, the authors of three, major international peer reviewed journals, and Takeda.

The integrated medical and statistical study report for the PROactive study was submitted to the EMEA for in-depth regulatory, medical, scientific and statistical assessment at the beginning of 2006. As this assessment would have entailed detailed evaluation by experienced and expert members of the agency over several months, their comments held particular importance in the assessment of the effect of Actos on cardiovascular outcomes.

Takeda explained that the PROactive study was a prospective, randomised, double-blind, multicentre, placebo-controlled, parallel group, phase 3b study involving 5238 with type 2 diabetes and a history of macrovascular disease. The study objectives were primarily; to demonstrate that Actos reduced mortality and macrovascular morbidity in high risk patients with type 2 diabetes compared with placebo and secondarily to further characterise the safety of Actos in this group of patients. The primary endpoint for the study was a composite of 7 different endpoints, 4 of which were disease-led (all cause mortality; non-fatal myocardial infarction (MI) including silent MI, acute coronary syndrome and stroke) and the remaining 3 were procedural (cardiac intervention, major leg amputation and bypass surgery or revascularisation of the leg). The principal secondary endpoint, time to the first occurrence of death from any cause, non-fatal MI (excluding silent MI) and stroke was again a disease-led endpoint, with the two other secondary end points being time to cardiovascular death and the individual components of the primary composite endpoint.

Takeda noted the complainant's comment that it was inappropriate link the results from the PROactive study with cardiovascular benefits because the primary outcome of the study did not reach statistical significance.

The letter stated that '5238 patients were randomised to pioglitazone or placebo in addition to existing and optimised therapies. Those who received pioglitazone showed a 10% relative risk reduction in the primary composite cardiac endpoints compared to placebo, although this did not reach statistical significance'. Thus it was clearly stated in the third paragraph, before any mention of the secondary endpoints, that the primary endpoint for the study was not achieved. Placing this statement first was done so as to comply with the guidance given for 'Advertising: presentation of clinical data' by the Medicines and Healthcare products Regulatory Agency (MHRA) in 2005 which specifically allowed for the promotional use of secondary end points in a study providing:

- The main study endpoint showed some difference in efficacy between the two treatment groups (for PROactive, there was a 10% difference in favour of Actos).
- Presentation of the secondary endpoints was placed within the context of the main primary endpoint (this has been done as stated above).
- The finding of the secondary endpoints were not weak (in PROactive even though all three secondary endpoints showed a beneficial trend in favour of Actos, only those which reached statistical significance were included in the letter).

The letter simply stated that the primary endpoint was not reached. However this finding was explored in more depth by both the PROactive Steering Committee in the initial publication of the study results as well as EMEA

which in the EPAR highlighted that the disease-led (and therefore more important end points) were in Actos' favour, as follows:

> 'Results of the primary composite endpoint analysis showed a 10% relative risk reduction of the first events within the composite for the pioglitazone-treated patients. The COX proportional hazards model gave an estimate of 0.90 for the hazard ratio comparing pioglitazone with placebo which did not reach statistical significance. However, within the primary composite endpoint, fewer disease endpoints (i.e. all cause mortality, non-fatal MI (excluding silent MI) silent MI, stroke, and ACS) were observed in the pioglitazone group, whereas the number of procedural endpoints (cardiac intervention, major leg amputation, leg revascularisation) varied between treatment groups. The only first event that occurred more frequently within the pioglitazone group was leg revascularisation. Overall, there were fewer total endpoints in the pioglitazone group (803) compared with placebo (900).'

Takeda further noted that the complainant had stated that the use of secondary endpoints in a negative study had been criticised by others.

The letter stated that pioglitazone significantly reduced the relative risk of the main secondary endpoint of all cause mortality, non-fatal MI (excluding silent MI) and stroke by 16% as well as two other pre-specified analyses which had been published in international, peer review journals, (Erdmann *et al*, 2007 and Wilcox *et al*, 2007) ie that pioglitazone significantly reduced the occurrence of recurrent MI by 28% (p=0.045) and the occurrence of a recurrent stroke by 47% (p=0.008).

These analyses were also considered by EMEA which commented in the EPAR that;

> 'Results of the analysis of the main secondary composite endpoint, a composite of 3 disease end points of the primary end point (i.e. all cause mortality, non-fatal MI (excluding silent MI) and stroke) showed a statistically significant 16% relative risk reduction of the events within the composite with pioglitazone treatment. The COX proportional hazards model gave an estimate of 0.84 (95% CI: 0.72, 0.98; p=0.0277) for the hazard ratio comparing pioglitazone with placebo…
>
> Subgroup analyses were performed on several pre-specified subgroups based on demographics, medical history, entry criteria, Baseline laboratory values and Baseline medications. The trend of benefit with pioglitazone on the primary and main secondary composite endpoints appeared to be consistent across the subgroups…
>
> Additional endpoints were analysed for the highest risk patients, those with prior MI or prior stroke. Pioglitazone showed a consistent trend of benefit over placebo among patients with prior MI for time to first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or stroke; cardiovascular death or non-fatal MI (excluding silent MI); and fatal or non-fatal MI (excluding silent MI). For patients with prior stroke, again pioglitazone showed consistent benefit over placebo for the time to first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or stroke cardiovascular death or stroke; and fatal and non-fatal stroke.'

Furthermore the EPAR referred to several additional analyses which were not mentioned in the mailer on the basis that they had either not been published in international peer review journals or that they were post-hoc and not pre-specified analyses. These were:

> 'Additional "measures of interest" including the composite endpoints of cardiovascular mortality, non-fatal MI (excluding silent MI) or stroke and fatal or non-fatal MI (excluding silent MI) showed statistically significant relative risk reductions of 18% and 23% respectively for pioglitazone-treated patients'
>
> 'The composite endpoints of all-cause mortality, MI (excluding silent MI), stroke, or ACS and of cardiovascular mortality, non-fatal MI (excluding silent MI), stroke or ACS were evaluated. Results of these post hoc analyses for pioglitazone-treated patients were consistent with those seen for the main secondary endpoint showing statistically significant reductions of 17% and 20% respectively, for these composite endpoints.'

Takeda referred to a number of cases where the Panel had reviewed the use of secondary endpoint data in promotional material in situations when the primary endpoint had failed to reach statistical significance. Together the cases supported the position that the results should be consistent across all the pre-defined endpoints, as was the case for the PROactive study. This position was in line with the 2005 guidance from the MHRA and suggested that the promotional use of selected, secondary analyses which did not achieve statistical significance, in the absence of any mention of the primary endpoint, was unacceptable. However, all of the cases suggested that balanced presentation of secondary analyses, alongside full disclosure of the results achieved for the primary endpoint, was acceptable.

In conclusion, even though the primary endpoint did not reach statistical significance Takeda considered it was justified and necessary to mention the beneficial effects which Actos had on some cardiovascular outcomes, in view of the large number of enquiries the company had received.

Takeda noted that following the presentation of the PROactive results at the EASD in 2005, a short article was published in the Education and Debate section of the BMJ (Freemantle). Being a statistician, the author's commentary concentrated on the statistical as opposed to the clinical considerations concerning PROactive, nonetheless he acknowledged the excitement felt by the audience of international diabetolgists when these results were first presented and commented that the 'Consensus of opinion following the presentation' was

that the 'Results would change clinical practice'. The article further stated 'Judgement should be reserved until the results are published in an academic journal' which indeed they were in the Lancet, JACC and Stroke (robust, well respected, peer-reviewed, academic journals) as well as in the new EPAR issued by EMEA. Since his original article, Freemantle had not commented further on the PROactive study.

Takeda noted that the complainant had stated that it was misleading to quote adverse effects from a reanalysis of the data rather than the results as originally published which showed an increase in heart failure, hospitalisation from heart failure, and death from heart failure.

The letter stated that while the incidence of serious heart failure was higher for the pioglitazone- treated v placebo-treated patients (5.7% v 4.1%), there was no increase in the incidence of death subsequent to a report of serious heart failure (1.5% v 1.4% respectively) and came from the primary analyses of the PROactive study, and not the sub-analyses. The primary analyses showed that while the incidence of serious heart failure was higher for Actos-treated patients v placebo (5.7% v 4.1%), there was no increase in the incidence of death due to heart failure with Actos (1.5% v 1.4% respectively). This was of particular importance, for whilst it was recognised that oedema and heart failure were side effects of glitazone therapy, the group of type 2 diabetics studied in the PROactive study were potentially particularly vulnerable to these specific adverse effects as they all had a history of macrovascular disease and almost 50% of them had had a previous MI and so were at risk of compromised cardiac function.

Together with the efficacy data, the safety data was also reviewed by the EMEA, following which a statement was added to section 5.1 of the Actos Summary of Product Characteristics (SPC) as follows 'Although there was an increase in oedema, weight gain and heart failure, there are no long term cardiovascular concerns with the use of pioglitazone and no increase in mortality from heart failure'. In addition, in order to ensure the optimal management of patients in this situation as well as allow for health professionals to make their own judgement as to its therapeutic value the precautionary statement from section 4.4 of the SPC that 'Patients should be observed for signs and symptoms of heart failure as pioglitazone is contraindicated in these patients' was also included. In conclusion the complainant was incorrect in their statements concerning Actos and heart failure.

Takeda noted that the complainant had stated that patients in the PROactive study did not have their cardiovascular medicine optimised - only 40% were on statins. The protocol specifically stated that all patients were to be treated according to the optimised standard of care at that site and in line with the recommendations given in the International Diabetes Federation European Region 1999 Guidelines. This meant that during the course of the study, at months 1, 2, 4, 6, 8, 10 and 12, and thereafter at six-monthly intervals, the investigators were required to optimise all therapy according to the Guidelines as follows; oral glucose-lowering medicine(s) if HbA_{1C}>6.5% and/or fasting venous plasma glucose >6.0mmol/L; insulin if HbA_{1C}>7.5%; a statin if LDL-cholesterol =3mmol/L; a fibrate if triglyceride >2.2mmol/L; lifestyle management followed by antihypertensive(s) if blood pressure >140/85mmHg.

Patients were recruited into the PROactive study between 2001 and 2002 ie before the introduction of the new General Medical Services (GMS) contract in the UK in 2003. Thus at the time, patients in the study were being more optimally managed than those in the general community in the UK, as the International Diabetes Federation Region 1999 Guidelines advocated similar guidance for diabetes dyslipidaemia to that which was later introduced in the GMS contract. The level of statin therapy was similar between groups at baseline (43%), and increased to a similar degree in both groups throughout the study (55% in the Actos-treated group and 55.5% in the placebo group at final visit, p=0.740). Other large, randomised, controlled trials conducted during a similar time period showed a similar trend with regard to the use of statins in patients with type 2 diabetes eg Kahn *et al*, (2006), which randomised patients between 1997 and 2001, showed lipid lowering agents were used in approximately a quarter of patients at baseline, increasing to 45.2%, 48.7% and 55.2% (glyburide, metformin and rosiglitazone groups respectively) at final visit. Furthermore, analysis of UK statin primary care prescribing for type 2 diabetics between 1999 and 2006 showed a similar trend.

Takeda noted the complainant's comment that in the group that was on statins, pioglitazone failed to show an advantage. Statistical analysis showed that baseline, statin-use or non-use, did not predict beneficial response to pioglitazone. The variability between the 25 predefined subgroups of baseline characteristics in terms of cardiovascular outcomes, including the use or non-use of statins at baseline, was no more than expected by chance alone. Therefore, the best estimate of treatment effect for any and all of the subgroups was the same as that for the entire PROactive cohort (Dormandy *et al*).

Dormandy *et al* conducted a multivariate analysis as well as univariate analyses on a number of covariates, including statin therapy. Both of these analyses showed that the trend towards benefit with Actos treatment showed no statistical difference for patients treated with /without existing statin therapy at baseline. Indeed EMEA specifically stated that:

> 'The results of the primary and main secondary endpoints were not affected by adjustment of significant baseline co variants (of which statin use was one) in a multivariate model.
>
> Subgroup analyses were performed on several pre-specified subgroups based on demographics, medical history, entry criteria, baseline laboratory values, and baseline medications. The trend of benefit with pioglitazone on the primary and main secondary composite endpoints appeared to be consistent across the subgroups.'

In conclusion the complainant's statement was not supported by any statistical analysis which had been published or was known to the company and was at odds with general medical, scientific, statistical and regulatory opinion.

Takeda noted that when the PROactive study was presented at the EASD in September 2005 the Association issued a press release which stated that the study:

> '… demonstrated that pioglitazone significantly reduces the risk of heart attacks (also known as myocardial infarction or MI), strokes and death in high risk patients with Type 2 Diabetes. This result is a breakthrough for these patients who are at high risk from heart attacks, strokes or premature death, as it is the first time that an oral diabetes medication has shown significant reductions in these macro-vascular events.'

In the EPAR the EMEA stated:

> 'While the treatment-group difference of 0.5% in the mean HbA_{1C} reduction was statistically significant, it likely cannot entirely explain the cardiovascular benefit noted for pioglitazone.
>
> In PROactive a significant reduction in major cardiovascular events of all-cause mortality, stroke, and myocardial infarction was observed for the pioglitazone-treated group. Events of serious heart failure were reported more frequently in the pioglitazone group than in the placebo group; however mortality was not increased in the pioglitazone-treated patients. A time-to-event analysis of serious heart failure in PROactive showed an increased risk of such an event in the pioglitazone group. However an analysis of time to first event of serious heart failure or all-cause mortality showed that there was no increased risk for this important outcome.'

Indeed even Freemantle stated that consensus of opinion following the presentation was that the 'Results would change clinical practice'.

In conclusion, Takeda stated that the complainant's statements were either factually incorrect, not supported by any statistical analysis, or at odds with the overwhelming medical, scientific, statistical and regulatory assessment of the data. Consequently the company denied that the 'Dear Healthcare Professional' letter at issue contained any misleading information, claims or comparisons or any information which was incapable of substantiation. The letter had been produced to high standards, had not brought the industry into disrepute, and was not in breach of the Clauses 7.2, 7.4, 9.1 or 2.

PANEL RULING

The Panel noted that the 'Dear Healthcare Professional' letter in question detailed some of the results from the PROactive study. At the outset the letter informed readers that the primary endpoint, the risk of a composite cardiac outcome, had not reached statistical significance although there was a trend in favour of pioglitazone v placebo. In that regard the Panel did not consider that the PROactive study was a 'negative' study as implied by the complainant. A benefit had been shown for pioglitazone, albeit one that was not statistically significant.

Having explained the primary outcome the letter proceeded to inform readers that pioglitazone significantly reduced the relative risk of the pre-defined main secondary endpoint, all-cause mortality, MI or stroke, by 16% (p=0.0273). The Panel considered that as the primary endpoint showed a trend in favour of pioglitazone, and the statistical significance of that endpoint had been explained at the outset, it was not misleading to give details of the secondary endpoint. The Panel did not consider the letter was misleading in that regard. No breach of Clause 7.2 was ruled.

The letter stated 'While the incidence of serious heart failure was higher for pioglitazone-treated vs placebo-treated patients (5.7% vs 4.1%), there was no increase in the incidence of death subsequent to a report of serious heart failure (1.5% vs 1.4%, respectively)'. The Panel noted Takeda's submission that these figures had come from the primary analysis of the PROactive study and not from a re-analysis as alleged by the complainant. The Panel noted the author's comment 'Consistent with the reported side-effect profile for pioglitazone, there was an increased rate of oedema and heart failure, though mortality due to heart failure did not differ between groups'. The Panel considered that the statement in the letter about heart failure was not misleading as alleged and could be substantiated. No breach of Clauses 7.2 and 7.4 was ruled.

The Panel noted the complainant's concern that only 40% of patients in the PROactive study were on statins and in that regard their cardiovascular therapy was not optimal. The report on the study (Dormandy *et al*) noted that study investigators were, however, required, throughout the study, to increase all therapy to an optimum according to the International Diabetes Federation European Region 1999 guidelines. Particular attention was drawn to the need to, *inter alia*, optimise lipid-altering therapy. The Panel noted that at baseline, patients in both the pioglitazone and the placebo group had LDL-cholesterol levels of 2.9mmol/L. In that regard the Panel did not consider that the patients in the PROactive study had not been optimally treated as alleged. The Panel also noted Takeda's submission that statistical analysis showed that baseline, statin-use or non-use, did not predict beneficial response to pioglitazone. This did not support the complainant's statement that, in the groups that were on statins, Actos failed to show an advantage. The Panel did not consider that the letter at issue was misleading in this regard. No breach of Clause 7.2 was ruled.

The Panel noted its rulings above and considered that there was no breach of Clauses 2 or 9.1.

Complaint received	**15 June 2007**
Case completed	**8 August 2007**

CASE AUTH/2012/6/07

GLAXOSMITHKLINE v TAKEDA

Competact mailer

GlaxoSmithKline alleged that in a Competact (pioglitazone and metformin) mailer, produced by Takeda, the claim 'Unlike other glitazone combination therapies, Competact costs LESS to prescribe than its constituent parts' was untrue. When the mailer was issued in January 2007 GlaxoSmithKline's product Avandamet (rosiglitazone and metformin) also cost less than its constituent parts.

GlaxoSmithKline further alleged that, despite inter-company dialogue on the matter, the mailer was used up until May 2007. Companies knowingly continuing to distribute incorrect information brought discredit upon and reduced confidence in the industry.

The Panel considered that the claim at issue was misleading and unfair as alleged. When the mailing was sent in January Avandamet also cost less than its component parts. A breach of the Code was ruled.

The Panel noted that the mailing had been sent on 2 January 2007 when a new Drug Tariff price for generic metformin had come into effect thus rendering the claim misleading and unfair. The Panel considered that by not checking the details in the January Drug Tariff prior to sending the mailing, Takeda had not maintained a high standard. A breach of the Code was ruled.

The Panel considered that in these circumstances the continued use of a claim acknowledged in inter-company correspondence to be in breach of the Code brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

GlaxoSmithKline UK Limited complained about a mailer (ref CM060811) for Competact (pioglitazone and metformin) produced by Takeda UK Limited. GlaxoSmithKline produced Avandamet (rosiglitazone and metformin).

COMPLAINT

GlaxoSmithKline stated that the mailing included the claim that Competact, one of two glitazone/metformin fixed-dose combination products on the UK market, and not the other, Avandamet, cost less than its component parts.

Fixed-dose combination preparations were the subject of some scrutiny by prescribers and prescribing advisers, as the cost to the NHS needed to be measured against the cost of their component parts prescribed separately. In this area this was especially pertinent as the price of generic metformin changed frequently according to market forces. The price of all reimbursable products was given in the Drug Tariff which was updated monthly, usually on the first of the month, with immediate effect.

The mailer in question had a date of preparation of January 2007, and GlaxoSmithKline understood from Takeda that it was first posted on 2 January to customers in several areas of the UK. GlaxoSmithKline was also aware of its use on several occasions across different parts of the UK since January.

In the mailer Takeda claimed that 'Unlike other glitazone combination therapies, Competact costs LESS to prescribe than its constituent parts'. This was not the case when the mailer was issued as Avandamet cost less than its single-constituent components.

During the inter-company dialogue Takeda had agreed that it used the Drug Tariff reimbursement price as the basis for the claim but had argued that the claim was correct up until immediately before the issue of the item. Takeda was correct in stating that the claim was accurate on 31 December 2006.

GlaxoSmithKline noted that apart from the three-month period from 1 October to 31 December 2006, during the twelve months, 1 June 2006 to 31 May 2007 inclusive, preceding this exchange, both Avandamet and Competact had cost the NHS less than their component parts prescribed separately. Takeda UK knew that the price of generic metformin had a recent history of being liable to fluctuation and that a new Drug Tariff price list would be published at the beginning of January. Despite this it sent out a mailer disparaging a competitor on the first working day of January without making adequate efforts to ensure that the claim was still correct and up-to-date.
The prominent statement that the date of preparation of the mailer was January 2007 reinforced the impression that the claim was correct in relation to the January 2007 Drug Tariff. Given the scrutiny of fixed dose combinations as mentioned above, once Takeda knew its claim was invalid it should have issued a corrective notice to all recipients of the mailer without waiting for a complaint from GlaxoSmithKline.

Copies of the online notification of changes to the Drug Tariff in January 2007, a record of the prices of generic metformin during the period June 2006 to June 2007, and a cost comparison of Avandamet versus its separate components for January 2007 were provided.

GlaxoSmithKline stated that with regard to the mailer at issue, despite extensive inter-company dialogue starting on 19 April it was aware of continued use of the mailer throughout the year, in a variety of locations

throughout the UK, up until May, in areas as widespread as Greater Manchester, Billericay, and Fife in Scotland. Takeda stated on 2 May that it was a one off mailer to a small distribution in one area only and was correct when it was mailed (this was not the case). However, on 16 May Takeda agreed in principle to issue a corrective notice to all the recipients of the mailer.

GlaxoSmithKline had asked Takeda to send that corrective letter to all recipients by 15 June with a copy to GlaxoSmithKline and notification to it that the corrective letter had been sent by 15 June.

In accordance with Code of Practice guidelines GlaxoSmithKline had set reasonable deadlines for completion of each stage of the process for reaching the agreed resolution of this issue. One month was more than adequate time to distribute a corrective letter for a mailing that had been in circulation since January 2007. This deadline had now passed without apology or explanation from Takeda.

A mailer such as the one at issue was a powerful way to communicate sensitive issues such as price. Recipients would expect that the information was factually correct and up-to-date. Companies mailing incorrect information and knowingly continuing to distribute it, brought discredit on the industry as a whole and served to reduce confidence in the industry.

GlaxoSmithKline alleged that the mailer was in breach of Clauses 7.2 and 7.3 of the Code. Takeda's failure to recognise its error and take timely corrective action with or without GlaxoSmithKline's intervention made its actions also in breach of Clause 9.1 and likely Clause 2.

While GlaxoSmithKline knew that the Panel had no power to impose sanctions on companies, it would urge that it considered in its ruling the impact of such continued activity in breach of the Code, and judge whether any further actions should be considered to redress the circulation of this factually inaccurate information.

RESPONSE

Takeda submitted that the mailer in question reminded prescribers about the efficacy and cost of Competact, which had recently been launched in the UK. GlaxoSmithKline initiated inter-company correspondence about the claim 'Unlike other glitazone combination therapies, Competact costs LESS to prescribe than its constituent parts' in April 2007 when both Competact and Avandamet were cheaper than their constituent parts. It became apparent that January Drug Tariff prices had changed and that Competact was £3.23 cheaper than its constituent parts, and Avandamet was 14p cheaper than its constituent parts. However when the piece was developed, Avandamet was 13p more than its component parts. Whilst acknowledging the error in pricing, Takeda considered this error was relatively small in that Avandamet was inadvertently portrayed as being more expensive than the cost of its component parts, arising through changes in the metformin price generated by the NHS Drug Tariff, unbeknown to Takeda. Importantly this error portrayed more a commercial issue, rather than jeopardising patient safety, as suggested by GlaxoSmithKline in its initial complaint, and did not make inappropriate clinical claims. Takeda had stopped using this claim and reassured GlaxoSmithKline as part of the inter-company dialogue.

Takeda had agreed to GlaxoSmithKline's request to send a corrective letter to all recipients of the mailer. Takeda had not agreed to GlaxoSmithKline's request to see the distribution list and review the letter prior to mailing. The last contact Takeda had from GlaxoSmithKline suggested that it had accepted Takeda's agreement. GlaxoSmithKline stated 'I trust that your undertaking will be to distribute the corrective letter to all lists who received the mailing – as you will not provide evidence of this – if GSK find that a corrective letter has not been received by one of the original recipients we will progress this complaint to the PMCPA. Once the above has been adhered to GSK will consider the matter closed'.

Takeda had done as agreed and sent the corrective mailer to all recipients of the original one. Takeda was in fact waiting to receive its final copies for its records and in order to send one to GlaxoSmithKline, when it received an email from GlaxoSmithKline stating that it had escalated this matter to the Authority. Takeda immediately emailed back to state that it considered this action inappropriate. The complaint to the Authority was dated the same day as Takeda had emailed GlaxoSmithKline as detailed above. This showed unwillingness on GlaxoSmithKline's part to resolve this matter at the inter-company level.

The mailer in question was produced shortly after the launch of Competact in the UK and was intended to remind prescribers that an advantage of Competact was that it was actually priced less than the sum of the cost of the constituent parts, and hence might be able to save the prescriber money.

Takeda had a different sales force structure to most pharmaceutical companies and as part of its regionalised structure each regional account director was able to develop materials for their own specific region and then have these approved by the usual certification process. The mailer in question was developed specifically for one regional account director. When GlaxoSmithKline raised its concern with Takeda its records showed that this was the only area that this was used in. Takeda subsequently found that it was used in several other areas but that this had not been recorded adequately in Takeda's approval system. Takeda acknowledged this to GlaxoSmithKline through inter-company dialogue when Takeda agreed to send a corrective mailer in all areas that the original mailer was sent. Furthermore, Takeda had ensured that its systems were robust in order to prevent a similar situation happening again.

The mailer was not mailed to anyone after this matter was identified. A revised version of the same mailer

was produced with the claim at issue deleted. GlaxoSmithKline had alleged that the item was in use in May; however this was not the case. The item was a mailer and as such was a one-off item that was mailed on a particular date. It was not an item that Takeda's regional account directors carried with them and distributed. At the time of writing this response GlaxoSmithKline had again only the day before reported that this letter was in use in May 2007. Takeda had checked its records and informed GlaxoSmithKline that this was not the case. Whilst Takeda awaited a copy of the mailer and evidence of the date it was in use, it had instigated a full investigation into the matter with its mailing house.

When this item was developed the price of generic metformin (£2.13 for 84 x 500mg tablets) had been stable for the whole time that Takeda had monitored it in preparation for the launch of Competact in the UK (October 2006 onwards). Takeda had not monitored the generic price before this time as the product was not licensed and hence Takeda was not developing materials.

This mailer was reviewed before Christmas but was not printed and subsequently posted until the first week in January. The date of preparation was changed to reflect the posting date in January without the generic prices being rechecked and this was an inadvertent process error. Takeda had fully investigated how this happened and had put processes in place to ensure it could not happen again. Hence Takeda did not know that the generic price for metformin had increased (to £2.33 for 84 x 500mg tablets) in January 2007 until GlaxoSmithKline raised this matter with it in April. This increase in price of metformin made Avandamet 14p cheaper than its constituent parts whereas for Competect the price difference was £3.23.

When this matter was raised by GlaxoSmithKline, Takeda gave a written undertaking to ensure that this claim was not in use on other materials and to ensure that it would not be used again. At the same time Takeda agreed to send a corrective mailer to all recipients of the original mailer.

Takeda accepted that an error had been made and it had taken this matter very seriously and had already put a process in place to ensure that would not occur again. However as stated this matter had already been resolved at the inter-company level and hence Takeda did not consider that it was appropriate for this to be forwarded to the Authority. Takeda refuted the allegation that it had breached Clauses 9.1 and 2.

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Following receipt of the response from Takeda regarding the above, the Director was concerned that GlaxoSmithKline's complaint did not meet the requirements of Paragraph 5.2 of the Constitution and Procedure. Paragraph 5.2 states, *inter alia*, that a complaint from a pharmaceutical company will be accepted only if the Director is satisfied that the company concerned has previously informed the company alleged to have breached the Code that it proposed to make a formal complaint and offered inter-company dialogue at a senior level in an attempt to resolve the matter, but that this offer was refused or dialogue proved unsuccessful.

In its response Takeda stated that it acknowledged its error, had stopped using the claim at issue and, as part of inter-company dialogue, reassured GlaxoSmithKline in this regard. It thus appeared that the requirements of Paragraph 5.2 had not been met ie the matter regarding the use of the claim at issue had been resolved. Takeda was longer using the claim 'Unlike other glitazone combination therapies, Competact costs less to prescribe than its constituent parts'.

GlaxoSmithKline had asked Takeda to take corrective action but this had not been done by the time GlaxoSmithKline sent its complaint to the Authority. Nonetheless, the claim at issue was no longer in use by Takeda and so in that respect the matter had been resolved. The Director could not accept a complaint on the basis that Takeda had not carried out sanctions requested by GlaxoSmithKline.

The Authority so informed GlaxoSmithKline.

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A further letter was received from Takeda stating that its investigation referred to in its response was now completed. GlaxoSmithKline informed Takeda on Monday 9 July that the mailer at issue was in use in a specific area of the UK. At that time Takeda checked its records and spoke to its mailing house and confirmed that this could not be correct as the mailer had not been posted since February.

GlaxoSmithKline had named the region and also the sales person alleged to be responsible. On the basis of this information a full investigation into the matter found a member of the sales team had gone outside of company standard operating procedures (SOPs) and guidance and had arranged for the mailer to be reprinted by a local printer and mailed in his region. This was absolutely unacceptable and had left Takeda in a regrettable situation whereby it had provided information to GlaxoSmithKline in good faith, only to then find that action had been taken by an individual which contradicted the information provided.

The investigation and subsequent disciplinary process was now underway with this individual. Takeda took such breaches of company SOPs and of the Code very seriously indeed.

Takeda had also issued a statement to all customer-facing staff on this matter and required each to sign the document to show that they had read and understood the instruction. It would also provide the additional training on this matter at the next company meeting.

Takeda was extremely disappointed that this had happened and that as a result of one individual's actions the company had been compromised. Takeda hoped that this letter demonstrated the seriousness of

this matter to the company and that appropriate action had been taken.

In response to a request for further information Takeda advised that the mailer was last sent out on 16 May.

PANEL RULING

The Panel noted that during inter-company correspondence with GlaxoSmithKline, Takeda had stated that the mailer was a one-off item. It had been posted in the first week of January. In its response to the Authority, Takeda again noted that the mailer was a one-off and submitted that it had stopped using the claim and that the mailer had not been sent to anyone after the matter was identified – which presumably was in April 2007 when inter-company correspondence began. Takeda denied that the mailer had continued to be used, as alleged by GlaxoSmithKline, in May 2007. However, in a subsequent letter to the Authority, Takeda stated that this was not so. Although not sent via the company's mailing house, a representative had had the mailing reprinted locally and mailed in his region. The Director considered that the continued use of the mailer meant that inter-company dialogue had been unsuccessful and therefore the complaint should proceed.

The Panel considered that the claim at issue 'Unlike other glitazone combination therapies, Competact costs LESS to prescribe than its constituent parts' was misleading and unfair. When the mailer was sent in January Avandamet also cost less than its component parts. Breaches of Clauses 7.2 and 7.3 were ruled.

The Panel noted that the mailer had been sent on 2 January when a new Drug Tariff price for generic metformin had come into effect thus rendering the claim misleading and unfair. The Panel considered that by not checking the details in the January Drug Tariff prior to sending the mailer, Takeda had not maintained a high standard. A breach of Clause 9.1 was ruled.

The Panel considered that in these circumstances the continued use of a claim acknowledged in inter-company correspondence to be in breach of the Code brought discredit upon and reduced confidence in the pharmaceutical industry. A breach of Clause 2 was ruled.

The Panel noted that Takeda had been seriously let down by one of its representatives. As the individual concerned had used a local printer to reproduce the mailer, Takeda had no record of its continued use and in this regard had, at first, given misleading information to both GlaxoSmithKline and the Authority. It appeared that until the identity of the individual had been revealed, Takeda had been unable to properly investigate the matter. Although seriously concerned about what had happened the Panel considered that, in the circumstances, it would not report Takeda to the Appeal Board under Paragraph 8.2 of the Constitution and Procedure.

Complaint received	**21 June 2007**
Case completed	**3 September 2007**

CONSULTANT IN PUBLIC HEALTH v PFIZER

Promotion of Champix

A lead consultant in public health at a primary care trust (PCT) alleged that the tactics Pfizer used to promote Champix (varenicline) were premature and unethical.

The complainant noted that Pfizer had organised a meeting for GPs, practice managers and, in particular, stop smoking advisors working in community pharmacies accredited by the local stop smoking service to provide stop smoking advice. Attendees received a pad of letters, clearly aimed at prescribers, which stated that the client was receiving a support programme from the local stop smoking service. Further promotion of Champix and the distribution of the letter had taken place in other local areas. This was clearly part of a concerted campaign.

The complainant was particularly concerned that the meeting had taken place before the publication of the definitive National Institute for Health and Clinical Excellence (NICE) guidance and thus in disregard of due process. The company had tried to ride roughshod over the gold standard therapy of nicotine replacement therapy (NRT), a determination that was currently unchanged by the draft NICE guidance. This meeting was organised without the courtesy of informing the local PCT or stop smoking service.

The Panel noted that Pfizer had organised a meeting in June 2007 to promote Champix to health professionals with an interest in smoking cessation. Champix had received its marketing authorization in September 2006 from when Pfizer was entitled to promote the product. It was immaterial in that regard that NICE had yet to issue guidance about the use of Champix. The Panel thus did not consider that Pfizer had prematurely promoted Champix. No breach of the Code was ruled.

The Panel noted that the slide kit used at the meeting in question did not refer to local guidelines and although it focussed on Champix it did, *inter alia*, detail the efficacy of NRT. The Panel thus did not consider that there was any evidence to show that Pfizer had either tried to wilfully obstruct locally agreed guidelines for the prescribing of medicines for smoking cessation, or tried to ride roughshod over the use of NRT as alleged. No breach of the Code was ruled.

The Panel noted that although Pfizer had not been in direct contact with the complainant it had talked to the team leader of the local stop smoking service who reported directly to the complainant. The Panel considered that Pfizer had consulted locally and had not acted without the courtesy of informing the local PCT or stop smoking service as alleged although the Code did not specifically require such actions. No breach of the Code was ruled.

A lead consultant in public health at a primary care trust (PCT), with responsibility for co-ordinating the local stop smoking service, complained about the promotion of Champix (varenicline) by Pfizer Limited.

COMPLAINT

The complainant alleged that Pfizer's tactics in relation to the promotion of Champix were premature and unethical. The company had organised a meeting for GPs, practice managers and in particular stop smoking advisors working in community pharmacies accredited by the local stop smoking service to provide stop smoking advice. Attendees received a pad of letters, clearly aimed at prescribers, which stated that the client was receiving a support programme from the local stop smoking service. Further promotion of Champix and the distribution of the letter had taken place in other local areas. This was clearly part of a concerted campaign.

The complainant was particularly concerned that: Champix had been promoted notwithstanding that the National Institute for Health and Clinical Excellence (NICE) had yet to definitely advise that it was an appropriate therapy ie the meeting had taken place before the publication of the definitive NICE guidance and thus in disregard of due process. Further, the complainant alleged that Pfizer sought to wilfully obstruct professionally determined, locally agreed guidelines for the prescribing of pharmacological interventions for stop smoking. Specifically the company had tried to ride roughshod over the gold standard of nicotine replacement therapy (NRT), a determination that was currently unchanged by the draft NICE guidance. Finally, the complainant noted that the meeting was organised without the courtesy of informing the local PCT or stop smoking service.

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

RESPONSE

Pfizer noted that the meeting in question, which was a follow on to other such meetings in the area, had been organised at the request of local health professionals with an interest in smoking cessation and included GPs, pharmacists, local smoking cessation advisors and nurses. The main objective of the meeting was to increase the awareness of Champix as a new form of treatment for smoking cessation in adult smokers.

During the meeting Pfizer made a presentation to the eighteen delegates using the Champix customer slide kit. This was an internally approved slide kit for use by the field force which had been pre-vetted by the Medicines and Healthcare products Regulatory Agency (MHRA). The slide kit detailed Champix's mechanism

of action, clinical data including comparative data, information about a patient support programme and ongoing clinical studies.

Before the presentation the delegates were given the 'GP referral aid' which was what Pfizer assumed the complainant had referred to and was used by the smoking cessation advisor and other health professionals during the appointment with the patient. By using the checklist provided the patients were assessed by the health professional. The tear-off aid sheet was then given to the patient and they were advised to give it to their GP at their next appointment. This review would help the GP when he/she examined the patient.

This process confirmed that the local stop smoking service had seen the patient and referred them to the GP. This ensured that the stop smoking service was being used properly, and further ensured that these patients would continue to receive the behavioural support from the service which formed an important part of the smoking cessation treatment approach with Champix.

As in every other meeting (seven in total including the one in question) for the local PCT, the locally agreed guidelines were not discussed, nor did any discussion take place on superiority over NRT. Pfizer representatives did discuss that where smokers might have failed on current therapies (NRT and Zyban (bupropion)) then Champix might be of benefit.

Pfizer had always behaved in a professional and sensitive manner, keeping in mind local guidelines, and would continue this professional approach in the future.

Pfizer noted that the meeting was held on 14 June 2007. Champix received its UK marketing authorization on 26 September 2006 which enabled it to start promoting the product to health professionals in accordance with Clause 3 of the Code. Pfizer ensured that it promoted its medicines within the ethical framework set by the Code. The intended audience for the meeting, as stated on the invitation, was NHS stop smoking services staff and other stakeholders interested in smoking cessation, specifically pharmacists, doctors and nurses who were responsible for providing smoking cessation advice and services in the region.

On 14 December 2006, the Department of Health circulated a best practice guidance document on the implementation of NICE guidance. The document reiterated, clarified and explained in more detail the original guidance relating to the introduction of new healthcare interventions and the funding direction applying to NICE technology appraisals. The document stated: 'It is not acceptable to cite a lack of NICE guidance as a reason for not providing treatment. A key role of the NHS is to make decisions about the use of new interventions and this has always been the case, long before NICE was established.'

Pfizer stated that for at least four of the seven meetings the local stop smoking service was invited to present its views. The team leader for the service, who reported directly to the complainant, attended the first meeting. As the stop smoking service team and locality leads had seen this presentation before and had not asked to see it again, they were not invited to the meeting on 14 June. This meeting was held for those team leaders and smoking cessation advisors that had not previously seen the presentation.

Pfizer had tried, unsuccessfully, several times to talk to the complainant. Based on this Pfizer kept in touch with the team leader of the local stop smoking service, and had always asked her to inform and invite the complainant to all of its meetings. Indeed, Pfizer had been in touch with all of the local stop smoking leads.

Pfizer considered that throughout it had behaved in an open and honest manner; it absolutely refuted the complainant's comments and regretted very much that he had chosen to express his views in this way. Pfizer had not promoted Champix outside its product licence and had complied with both the spirit and the letter of the Code. Pfizer concluded that it had not breached Clause 9.1 or Clause 2 and it was confident that its conduct had been of a high standard throughout.

PANEL RULING

The Panel noted that Pfizer had organised a meeting in June 2007 to promote Champix to health professionals with an interest in smoking cessation. Champix had received its marketing authorization in September 2006 from when Pfizer was entitled to promote the product. It was immaterial in that regard that NICE had yet to issue guidance about the use of Champix. The Panel thus did not consider that Pfizer had prematurely promoted Champix. No breach of Clause 9.1 was ruled.

The Panel noted that the slide kit used at the meeting in question did not refer to local guidelines and although it focussed on Champix it did, *inter alia*, detail the efficacy of NRT. The Panel thus did not consider that there was any evidence to show that Pfizer had either tried to wilfully obstruct locally agreed guidelines for the prescribing of medicines for smoking cessation, or tried to ride roughshod over the use of NRT as alleged. No breach of Clause 9.1 was ruled.

The Panel noted Pfizer's submission that although it had not been in direct contact with the complainant it had talked to the team leader of the local stop smoking service who reported directly to the complainant. The Panel considered that Pfizer had consulted locally regarding its promotional activities and intent and that it had not acted without the courtesy of informing the local PCT or stop smoking service as alleged although the Code did not specifically require such actions. No breach of Clause 9.1 was ruled.

The Panel noted its rulings above and considered that there was no reason to rule a breach of Clause 2 of the Code, a ruling which was a sign of particular censure and reserved for such use.

Complaint received	**28 June 2007**
Case completed	**15 August 2007**

CASE AUTH/2015/7/07

LILLY v BAYER SCHERING PHARMA

Promotion of Levitra

Lilly complained about a journal advertisement and a leavepiece for Levitra (vardenafil) issued by Bayer Schering Pharma. The claim 'Works first time in 9 out of 10 men' appeared in both items referenced to Valiquette *et al* (2005) and qualified, in small print, by 'Successful response rates (SEP2) were clearly demonstrated in the majority of [erectile dysfunction] patients'.

Lilly noted from the study that during the challenge phase, the proportion of patients with a first-time success based on SEP2 was 87%; of these patients, 85% had maintenance of erection (SEP3) sufficient for completion of intercourse, leading to a first-time SEP3 success of 74% of patients. Lilly believed equating 87% success in SEP2 from the challenge phase of this study to 9 out of 10 men achieving successful sexual intercourse with their first vardenafil tablet was an inaccurate and misleading interpretation.

Further, the one week challenge phase was conducted as an open label study; however this was not mentioned in the advertisement nor the leavepiece as an important and clinically relevant study limitation or bias.

The Panel noted that during the open-label challenge phase 520/600 patients given a single dose of Levitra 10mg achieved SEP2 success ie penetration. Although in both the advertisement and the leavepiece a footnote to the claim noted that success was measured as achievement of SEP2, there was no mention that this meant penetration and in any event it was a principle under the Code that claims should not be qualified by the use of footnotes and the like. The Panel considered the impression given by the claim 'Works first time in 9 out of 10 men' was that for 90% of men, their first dose of Levitra resulted in successful intercourse (SEP3) and not just successful penetration (SEP2). This impression was endorsed by the claim 'Get it right first time' in the leavepiece and the strapline 'Right first time' in the advertisement. Further, the data 520/600 did not equate to 9 out of 10. The Panel ruled that the claim was misleading and had not been substantiated in breach of the Code.

Lilly alleged that the claim 'Levitra lets them wine and dine' in the leavepiece referenced to the summary of product characteristics (SPC) was misleading as it was inconsistent with the SPC.

The Panel noted that the SPC stated that Levitra could be taken with or without food and that the onset of activity might be delayed with a high fat meal. The Panel noted that Levitra 20mg did not potentiate the effects of alcohol (mean blood level of 73mg/dl) on blood pressure and heart rate and the pharmacokinetics of Levitra were not altered. The Panel noted that in this regard the blood alcohol limit for driving was 80mg/dl. The Panel considered that given the content of the SPC insufficient information had been given in the leavepiece about the effect of food and drink. In that regard the claim 'Levitra lets them wine and dine' was misleading and a breach of the Code was ruled.

The claim 'Given a choice of PDE5 inhibitors, Levitra is the one many men prefer' appeared in the leavepiece referenced to an abstract presented by Sommer *et al* at a North American congress in 2005. Lilly believed that the Sommer *et al* abstract had not been peer reviewed and noted that the limitations of the study were not stated in the leavepiece; hence the claim of preference was misleading and unfair. Lilly noted that in Case AUTH/1638/10/04 Bayer had been ruled in breach of the Code for using this preference claim from this same study. Lilly alleged that the use of this claim again was a breach of the Code.

The Panel noted that the Sommer abstract provided little information about the design and analysis of the study which compared preferences for vardenafil, sildenafil and tadalafil (Lilly's product Cialis) at maximum and half maximum doses. Levitra had been the preferred treatment at maximum and half maximum doses. At maximum dose 39% of patients preferred Levitra with 22% preferring sildenafil and 38% preferring tadalafil. The corresponding figures at half maximum doses were 44%, 37% and 19%.

The Panel noted the difference in preference expressed for the products. It did not appear that there had been any statistical evaluation of the results. The Panel queried whether a difference of 39% of patients preferring vardenafil compared with 38% preferring tadalafil at maximum approved doses represented a true difference between the two products particularly in the absence of any statistically significant difference. The Panel considered that, based upon the results of Sommer *et al* (2005), the claim was misleading and unfair and breaches of the Code were ruled.

Eli Lilly and Company Limited complained about the promotion of Levitra (vardenafil) by Bayer Schering Pharma. The items at issue were a journal advertisement (ref 7LEVI05) and a leavepiece (ref 7LEVI07). Lilly supplied Cialis (tadalafil).

1 'Works first time in 9 out of 10 men'

This claim appeared in both items and was referenced to Valiquette *et al* (2005). On each piece the claim was qualified, in small print, by 'Successful response rates

(SEP2) were clearly demonstrated in the majority of [erectile dysfunction] patients'.

COMPLAINT

Lilly stated that the efficacy section of Valiquette *et al* stated that during the challenge phase of the study, the proportion of patients with a first-time success based on SEP2 was 87% (520/600 patients); of these patients, 85% had maintenance of erection (SEP3) sufficient for completion of intercourse, leading to a first-time SEP3 success of 74% of patients.

Lilly believed equating 87% success in SEP2 from the challenge phase of this study to 9 out of 10 men achieving successful sexual intercourse with their first vardenafil tablet was an inaccurate and misleading interpretation.

Further, the one week challenge phase of this study was conducted as an open label study; however this was not mentioned in the advertisement nor the leavepiece as an important and clinically relevant study limitation or bias.

Lilly therefore alleged that the advertisement and the leavepiece were in breach of Clauses 7.2 and 7.4 of the Code.

RESPONSE

Bayer Schering stated whilst the percentages quoted by Lilly were correct, the conclusions drawn were incorrect. Bayer Schering had never claimed that SEP2 (penetration) success equated to successful intercourse which was assessed by SEP3 (maintenance). Therefore any suggestion that Bayer Schering had made this claim (ie that SEP2 penetration equated to full successful intercourse) was based on an incorrect interpretation. All Bayer Schering's materials with this claim specifically stated that SEP2 was the measure referred to.

Bayer Schering noted that Lilly was further concerned that the one week challenge phase of Valiquette *et al* was conducted as an open label study, but that this was not mentioned in the advertisement nor the leavepiece as an important and clinically relevant study limitation or bias. Bayer Schering submitted that the open label challenge phase was neither a limitation nor a source of bias but rather a critical part of the study which was designed to examine the extent to which efficacy was sustained over a 12 week treatment period. In order to do this it was necessary to identify responders to treatment with vardenafil and exclude placebo responders. Furthermore the study was fixed at the initial vardenafil starting dose and was not a flexible dose design. Flexible dose studies of vardenafil were invariably associated with higher efficacy rates. After the open label challenge phase vardenafil responders were randomised to either placebo or vardenafil. At this point it was important that the study was double-blind in order to exclude any potential bias of assessment. In an attempt to resolve this point of dispute Bayer Schering offered to add 'Data from challenge phase of open label study' which would add further clarity to this claim. Bayer Schering had instigated this already for all future materials.

PANEL RULING

The Panel noted that during the open-label challenge phase of Valiquette *et al* 520/600 patients given a single dose of Levitra 10mg achieved SEP2 success ie penetration. Although in both the advertisement and the leavepiece a footnote to the claim noted that success was measured as achievement of SEP2, there was no mention that this meant penetration and in any event it was a principle under the Code that claims should not be qualified by the use of footnotes and the like. The Panel considered the impression given by the claim 'Works first time in 9 out of 10 men' was that for 90% of men, their first dose of Levitra resulted in successful intercourse (SEP3) and not just successful penetration (SEP2). This impression was endorsed by the claim 'Get it right first time' in the leavepiece and the strapline 'Right first time' in the advertisement. Further, the data 520/600 did not equate to 9 out of 10. The Panel ruled that the claim was misleading and had not been substantiated in breach of Clauses 7.2 and 7.4.

2 'Levitra lets them wine and dine'

This claim appeared in the leavepiece and was referenced to the Levitra summary of product characteristics (SPC).

COMPLAINT

Lilly considered that the claim was inconsistent with the SPC which stated 'The onset of activity may be delayed if taken with a high fat meal'. Lilly alleged that the claim was misleading in breach of Clause 7.2.

RESPONSE

Bayer Schering did not accept that the claim was inconsistent with the SPC. Section 4.2 of the SPC, Posology and method of administration, stated that Levitra could be taken with or without food.

The changes in pharmaocokinetics of vardenafil when taken with a high fat meal gave rise to the statement in the posology section 'The onset of activity may be delayed if taken with a high fat meal'. Section 5.2 expanded on this: 'When vardenafil is taken with a high fat meal (containing 57% fat), the rate of absorption is reduced, with an increase in the median tmax of 1 hour and a mean reduction in Cmax of 20%. Vardenafil AUC is not affected. After a meal containing 30% fat, the rate and extent of absorption of vardenafil (tmax, Cmax and AUC) are unchanged compared to administration under fasting conditions'.

The Levitra SPC stated that there were no effects on vardenafil's absorption when taken with a meal containing 30% fat. This was the fat content of a typical evening meal.

The relatively low absolute bioavailability of vardenafil and metabolism predominantly via CYP3A4 isoenzymes led to high inter- and intra-individual

variability. The inter-individual variability for Cmax and AUC was 38-59% and 37-51% respectively. The intra-individual (within subject) variability for Cmax and AUC was approximately 20% and 31% respectively. The median (range) tmax hr following a high fat meal (57% fat) was 2.0 (0.5-4.0) and after a typical evening meal (30% fat) 1.0 (0.5-4.0). These changes in primary pharmacokinetics were not considered clinically significant and indicated that exposure to vardenafil was not affected by the consumption of meals that contained high or moderate amounts of fat. Hence the SPC statement that vardenafil could be taken with and without food.

With regard to the effect of alcohol on Levitra, section 4.5 of the SPC stated that 'When vardenafil (20mg) and alcohol (mean maximum blood alcohol level of 73mg/dl) were taken together, vardenafil did not potentiate the effects of alcohol on blood pressure and heart rate and the pharmacokinetics of vardenafil were not altered'.

PANEL RULING

The Panel noted that the Levitra SPC stated that Levitra could be taken with or without food and that the onset of activity might be delayed with a high fat meal.

The Panel noted that Levitra 20mg did not potentiate the effects of alcohol (mean blood level of 73mg/dl) on blood pressure and heart rate and the pharmacokinetics of Levitra were not altered. The Panel noted that in this regard the blood alcohol limit for driving was 80mg per 100mls.

The Panel considered that given the content of the SPC insufficient information had been given in the leavepiece about the effect of food and drink. In that regard the claim 'Levitra lets them wine and dine' was misleading and a breach of Clause 7.2 was ruled.

3 'Given a choice of PDE5 inhibitors, Levitra is the one many men prefer'

This claim appeared in the leavepiece and was referenced to an abstract presented by Sommer *et al* at a North American congress in 2005.

COMPLAINT

Lilly believed that the Sommer *et al* abstract had not been peer reviewed and noted that the limitations of the study were not stated in the leavepiece; hence the claim of preference was misleading and unfair. Lilly noted that in Case AUTH/1638/10/04 Bayer had been ruled in breach of Clauses 7.2 and 7.3 for using this preference claim from this same study, in a poster at the BAUS meeting of 2004. Lilly believed the use of this claim again was a breach of Clauses 2, 7.2 and 7.3.

RESPONSE

With regard to Case AUTH/1638/10/04 Bayer Schering submitted that the ruling of a breach of the Code was in relation to the promotional use of Sommer *et al* poster (ie without prescribing information) and not the data per se. It was important to understand the data on that earlier poster were the interim results.

The data used in Bayer Schering's current promotional pieces were now final data, presented as an abstract at the North American Congress of the Ageing Male 2005. Abstracts (with the author(s) anonymised) would have been peer reviewed before acceptance at a congress. Mulhall and Montorsi (2005) reviewed preference trials and demonstrated that Sommer *et al*, unlike some others, had many of the attributes of a well designed preference trial.

PANEL RULING

The Panel noted that the Sommer abstract provided little information about the design and analysis of the study which compared preferences for vardenafil, sildenafil and tadalafil (Lilly's product Cialis) at maximum and half maximum doses. Levitra had been the preferred treatment at maximum and half maximum doses. At maximum dose 39% of patients preferred Levitra with 22% preferring sildenafil and 38% preferring tadalafil. The corresponding figures at half maximum doses were 44%, 37% and 19%.

The Panel noted Bayer Schering's submission regarding the basis of the Appeal Board's rulings in Case AUTH/1638/10/04. Although in that case the promotional use of the Sommer poster had been ruled in breach of the Code because of a lack of prescribing information, it had also been ruled in breach of the Code for the data per se. The Appeal Board had considered that the poster was misleading because it did not clearly state the length of the study period and nor did it make it sufficiently clear that only interim results were presented, the study, at that time, was still ongoing.

Turning to the case now before it, the Panel noted that the study had been completed. The Panel noted the difference in preference expressed for the products. It did not appear that there had been any statistical evaluation of the results. The Panel queried whether a difference of 39% of patients preferring vardenafil compared with 38% preferring tadalafil at maximum approved doses represented a true difference between the two products particularly in the absence of any statistically significant difference. The Panel considered that, based upon the results of Sommer *et al* (2005), the claim was misleading and unfair and breaches of Clauses 7.2 and 7.3 were ruled.

The Panel did not consider the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of censure and reserved for such use.

Complaint received	**9 July 2007**
Case completed	**17 August 2007**

CASE AUTH/2016/7/07

NOVARTIS v BRISTOL-MYERS SQUIBB

Sprycel leavepiece

Novartis complained about a Sprycel (dasatinib) leavepiece issued by Bristol-Myers Squibb. Sprycel was indicated for use in patients with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including Novartis' product Glivec (imatinib).

Novartis stated that the four page spread of the leavepiece juxtaposed 'Selectivity' claims for Sprycel with claims about 'Sustainability' and 'Strength'. Under the 'Selectivity' heading Novartis noted the following bullet points: 'Sprycel also targets other oncogenic pathways such as c-KIT, Ephrin receptor kinase, PDHF ß receptor'; 'Sprycel is the first and only therapy to bind to both active and inactive conformations of the BCR-ABL'; 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*' and 'Sprycel is active against all BCR-ABL mutations tested, except T315I'. Whilst no specific efficacy claims were made, the juxtaposition of the 'Selectivity' section misleadingly implied that dasatinib's different mechanism of action referred to in the bullet points correlated with clinical benefits; however such implications were not supported by clinical data. Novartis further alleged that the subheading 'Sprycel has a different mechanism of action' was a hanging comparison.

Novartis noted that the selectivity page referred to three oncogenic pathways targeted by Sprycel and alleged that these could not be considered selective. Further more some of the pathways were specifically associated with tumours other than CML. The citing of dasatinib's targeted activity in respect to these pathways, under a heading of selectivity, next to claims on sustainability and strength of action, implied an unproven and unlicensed clinical activity in tumours expressing these pathways. At best this was misleading and at worst was promotion outside the Sprycel marketing authorization.

With regard to the bullet point 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*', Novartis knew of no CML guidelines that cited the greater potency of dasatinib compared to imatinib as conferring superior efficacy. Furthermore, at the clinical doses prescribed, the superior potency *in vitro* of dasatinib did not confer any comparative benefits with respect to its side-effect profile (indeed, initial clinical data might suggest the contrary) nor its comparative cost with imatinib 400 or 600mg.

The Panel noted that the leavepiece was entitled 'Sprycel Chronic phase CML For imatinib resistant or intolerant patients'. Page 2 was headed 'Sprycel in Chronic phase', and pages 2, 3 and 4 all referred to imatinib resistant CML patients. It was thus in this context that page 5, headed 'Selectivity', would be read.

The Panel did not consider that, grammatically, the claim 'Sprycel has a different mechanism of action' was a hanging comparison. Further, the Panel considered that given the content of the previous pages, and the title of the leavepiece, it would be obvious to the reader that the claim compared Sprycel with imatinib. No breach of the Code was ruled.

The Panel noted that the claim 'Sprycel also targets other oncogenic pathways such as: c-KIT, Ephrin receptor kinases, PDGF ß receptor' was referenced to the summary of product characteristics (SPC). Section 5.1 stated that dasatinib inhibited the activity of the BCR-ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases and PDGF ß receptor. Although such pathways were implicated in malignancies other than CML the claim at issue was in a leavepiece specifically targeted at CML. Given the context in which it appeared the Panel did not consider that the claim implied that Sprycel had clinical activity in any condition other than CML. The claim was neither misleading in that regard and nor did it promote the use of Sprycel beyond its SPC. The Panel considered that whilst the page was headed 'Selectivity' there was no actual claim that Sprycel was selective. Another page stated, beneath the heading 'Selectivity' that Sprycel offered a new multi-targeted mechanism of action. No breach of the Code was ruled.

The Panel noted that the subheading 'Sprycel has a different mechanism of action' was asterisked to the footnote, 'Based on *in vitro* data' which appeared in small, grey typeface, at the bottom of the page. The Panel considered that, except for 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*', it was not clear from the outset that all the other claims at issue were based on *in vitro* data. Readers would assume that they related to the clinical situation which was not so. No data had been submitted to show the relevance of the claims to clinical practice. Bristol-Myers Squibb had submitted that the bullet points on page 5 'listed the possibilities' with regard to the product's mechanism of action. This was not entirely clear from the leavepiece. The Panel considered that, given the context in which they were made, the claims 'Sprycel is the first and only therapy to bind to both active and inactive conformations of BCR-ABL' and 'Sprycel is active against all BCR-ABL mutations tested, except T315I' were misleading as alleged; both were ruled in breach of the Code.

The Panel noted that the claim 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*' was not a claim for superior potency in relation to weight as alleged. Nonetheless, Bristol-Myers Squibb had not submitted any data to show what relevance this *in vitro* data had in clinical practice. The company submitted that it was one of a number of possible mechanisms of action for Sprycel which might explain its efficacy in imatinib resistant patients. The Panel did not consider this was entirely clear from the leavepiece as noted above. The clinical relevance of the data was not sufficiently clear to the reader. The Panel considered that the claim was misleading in this regard. A breach of the Code was ruled.

Novartis Pharmaceuticals UK Ltd complained about a leavepiece (ref DAS/1106/0146/1008) for Sprycel (dasatinib) issued by Bristol-Myers Squibb Pharmaceuticals Limited. Sprycel was indicated for use in patients with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including Novartis' product Glivec (imatinib).

The leavepiece at issue was folded concertina like and unfolded to reveal eight 'pages'. The four pages on one side of the leavepiece were successively headed 'Sprycel in Chronic Phase', 'Strength', 'Sustainability' and 'Selectivity'. It was the last page headed 'Selectivity' which was the subject of complaint.

Bristol-Myers Squibb voluntarily withdrew the leavepiece in April 2007 and informed Novartis by email on 12 April.

COMPLAINT

Novartis stated that the Sprycel leavepiece described the features of the product in an open 4-page spread which juxtaposed 'Selectivity' claims for the product with 'Sustainability' and 'Strength' claims. Whilst no specific efficacy claims were made in the 'Selectivity' section, the juxtaposition of this section was misleading as it implied that dasatinib's different mechanism of action correlated with clinical benefits; however this claim was not supported by clinical data. Furthermore, the subheading 'Sprycel has a different mechanism of action' appeared to be a hanging comparison, in breach of Clause 7.2 of the Code as no comparative data was presented in support.

The second bullet point on the 'Selectivity' page, 'Sprycel also targets other oncogenic pathways such as:' presented three biological features related to dasatinib, which targeted other oncogenic pathways c-KIT, ephrin receptor kinases and PDGF ß receptor. This claim was a non-sequitur from the heading 'Selectivity'. By definition, targeting three oncogenic pathways could not be considered selective.

Whilst these biological features were certainly of biological relevance, the bulleted points were unsupported by any reference to clinical data generated with dasatinib in tumours specifically expressing, for example, c-KIT (such as gastro-intestinal stromal tumours). Novartis acknowledged that the lack of a marketing authorization for Sprycel in tumours where these other oncogenic pathways were implicated absolutely prohibited any promotion of its therapeutic use in these tumour types. That said, the citing of dasatinib's targeted activity in respect to these three pathways, under a heading of selectivity, and then juxtaposed with sustainability and strength of action, implied either overtly or covertly, and deliberately or inadvertently, an unproven and unlicensed clinical activity in tumours expressing these pathways. At best this was misleading and at worst constituted promotion outside the Sprycel marketing authorization and a breach of Clause 3.2 was alleged.

The third bullet point under the heading 'Selectivity' stated 'Sprycel is the first and only therapy to bind to both active and inactive conformations of the BCR-ABL'. Whilst chemically this might currently be true, it implied that this structural feature conferred clinical benefit. However, no correlation had been clinically proven between the clinical activity of dasatinib and its binding profile. As the leavepiece failed to make this point clear, this statement was alleged to be misleading in breach of Clause 7.2.

With regard to the fourth bullet point 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*', Novartis noted the supplementary information to Clause 7.2 which stated: 'Claims for superior potency in relation to weight are generally meaningless and best avoided unless they can be linked with some practical advantage, for example, reduction in side-effects or cost of effective dosage'.

In this context, Novartis knew of no CML guidelines that cited the greater potency of dasatinib compared to imatinib as conferring superior efficacy. Furthermore, at the clinical doses prescribed, the superior potency *in vitro* of dasatinib most certainly did not confer any comparative benefits with respect to its side-effect profile (indeed, initial clinical data might suggest the contrary) nor its comparative cost with imatinib 400 or 600mg. Novartis alleged that the claim was in breach of Clause 7.2.

The last bullet point on the 'Selectivity' page, 'Sprycel is active against all BCR-ABL mutations tested, except T315I' presented the same issues as those set out above in that the claim implied a clinical benefit but with no clinical data presented in imatinib-resistant patients due to non-T315I mutations. Novartis thus alleged that the claim was misleading by inference, in breach of Clause 7.2.

RESPONSE

Bristol-Myers Squibb explained that CML was an unusual leukaemia in that it was associated with a specific chromosomal abnormality, the Philadelphia chromosome. This abnormal chromosome contained an aberrant fusion oncogene called BCR-ABL. This gene encoded the Bcr-Abl oncoprotein, which was a tyrosine protein kinase and which was believed to be both necessary and sufficient for the onset of this malignant condition. The treatment of CML was revolutionised

by the introduction of imatinib several years ago. Until then the existing therapies (such as hydroxyurea and interferon-alpha) were only partially successful in controlling the disease. Bone marrow transplantation (BMT) was a potential cure but the mortality associated with it was such that it was reserved only for the most fit of patients. Most CML patients were older than 60 years of age and were generally not fit for BMT.

Imatinib was a tyrosine kinase inhibitor specifically targeted against the Bcr-Abl oncoprotein. It led to lasting clinical and cytogenetic responses and greatly improved patients' quality of life. Unfortunately, some patients proved resistant to its effect and others proved intolerant of imatinib. The resistance could be primary resistance (ie that a patient upon first exposure to imatinib did not respond) or secondary resistance (ie that a patient initially responded to imatinib but eventually relapsed). The reasons for resistance to imatinib were multi-factorial and included mutations in the tyrosine kinase domain of the BCR-ABL gene and over-expression of the BCR-ABL gene. There were also BCR-ABL independent mechanisms of resistance. These latter mechanisms included clonal evolution, where the need for molecular drive by Bcr-Abl was circumvented and also mechanisms that altered the intracellular concentrations of imatinib, for example by the over-expression of efflux pumps.

Accordingly, there was still an unmet medical need for CML patients resistant or intolerant to imatinib. Sprycel was developed to address this need. It was licensed in November 2006 for 'adults with chronic, accelerated or blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib mesilate'.

The leavepiece was intended to be left with health professionals following an introductory discussion on Sprycel with Bristol-Myers Squibb representatives. It was a two-sided item but was folded in a manner which created four pages on either side.

Page 1 was the 'title' page. Upon opening the folded leavepiece and turning over from the title page, then pages 2, 3, 4, and 5 became apparent. The page at issue, page 5, was headed 'Selectivity' and was to be read in the context of the three other pages (2, 3, and 4, headed 'Sprycel in Chronic Phase', 'Strength' and 'Sustainability', respectively).

Pages 2, 3 and 4 introduced the CML indication for Sprycel and noted that Sprycel represented the first treatment for imatinib resistant or intolerant patients. The clinical efficacy of dasatinib in such patients was displayed in pages 3 and 4.

With regard to the claim 'Sprycel has a different mechanism of action' Bristol-Myers Squibb noted that the mechanism of action of a medicine was an allowable item to be addressed in any leavepiece and was an especially important element in a leavepiece which introduced a new medicine designed to overcome a deficiency in an existing well-established one.

Manifestly, if a new medicine was specifically designed and clinically proven to overcome resistance to an established one, then the new medicine must be acting in a different way. If the new medicine had exactly the same mechanism of action, then it would not be expected to overcome the resistance engendered to the established medicine. Stating that Sprycel had a different mechanism of action was thus an important point of education.

It was clear from the layout of the leavepiece (ie that page 5 was to be viewed in conjunction with pages 2, 3, and 4) and from the content of pages 2, 3 and 4 that Sprycel's mechanism of action was being compared with that of imatinib. The grammatical form of a 'hanging comparison' was wording such as 'better' or 'stronger'. The claim at issue was not of this form. Accordingly, Bristol-Myers Squibb denied that this claim was a hanging comparison and denied that it was in breach of Clause 7.2.

Sprycel had been shown in clinical studies to be effective in patients with imatinib resistance. The clinical studies leading to the grant of the marketing authorization included patients with imatinib resistance irrespective of the presumed cause of the resistance. Some of the key efficacy results of these studies were summarised in this leavepiece.

The five bullet points on page 5 listed the known pharmacology of dasatinib which in sum explained its ability to be effective in CML patients resistant to imatinib. It should be remembered, therefore, when considering the individual allegations below, that Sprycel's multiple mechanisms of action were such that, collectively, they were responsible for the product's efficacy against the possible multiple reasons for imatinib resistance.

With regard to the allegations about the claim 'Sprycel also targets other oncogenic pathways such as:' Bristol-Myers Squibb reiterated that there were many possible mechanisms for resistance to imatinib and it was difficult to determine which precise mechanism (or combination of mechanisms) was responsible in any one patient. In approximately half of patients, it was generally accepted that the most likely cause of resistance was point mutations of the BCR-ABL gene such that the local topology of the Bcr-Abl oncoprotein was altered at the molecular level, meaning that imatinib could no longer bind with adequate affinity and thus no longer inhibit oncoprotein activity. However, no such obvious reason was apparent for the remainder of resistant CML patients.

Accordingly, for a single medicine to be effective in a patient with imatinib resistance, it must be able to counter the effects of mutations but must also be able to act against the many other possible causes.

In *in vitro* tests, dasatinib had been shown to have a range of pharmacological activities. These included being a tyrosine kinase inhibitor. Indeed, *in vitro* tests showed it to be 325 times more potent than imatinib in inhibiting BCR-ABL. It was also an SRC kinase inhibitor and was active in a range of other oncogenic

pathways as shown in the leavepiece. It had been shown to be active against a wide range of BCR-ABL mutations (but not the T315I mutation). Whilst Bristol-Myers Squibb could acknowledge that certain of dasatinib's mechanisms of action might be pertinent to non-CML indications, the possible mechanisms of action of dasatinib listed in this leavepiece had the potential to counter certain possible mechanisms of imatinib resistance in CML, particularly in advanced disease.

Accordingly, in a CML leavepiece explaining the pharmacology of the product, it was pertinent to refer to these possible mechanisms of action, even though they might also have some meaning in other disease contexts.

Since all of the listed mechanisms had pertinence to CML, and appeared in a leavepiece which only referred to CML, Bristol-Myers Squibb refuted the allegation of promotion outside of Sprycel's licence, and denied any breach of Clause 3.2.

Bristol-Myers Squibb noted that Novartis accepted the validity of the underlying molecular biology of the claim 'Sprycel is the first and only therapy to bind to both the active and inactive conformations of BCR-ABL'. As above, this was but one possible mechanism of action for Sprycel which might explain its efficacy in imatinib resistant patients, and it was not presented as being wholly responsible for its clinical efficacy in these patients. That this was the case was apparent from the layout of the text on page 5. The subheading referred to 'mechanism of action' and then there were bullet points, including this one, which listed the possibilities.

Bristol-Myers Squibb noted that Novartis quoted the supplementary information to Clause 7.2 which cautioned that 'claims for superior potency in relation to weight are…best avoided unless they can be linked with some practical advantage, for example, reduction in side-effects or cost of effective dosage' (emphasis added by Bristol-Myers Squibb). However, the claim 'Sprycel is 325 fold more potent than imatinib' was not a claim for superior potency 'in relation to weight', and so did not represent the type of claim to which this section of the supplementary information was addressed.

Bristol-Myers Squibb referred to the superior potency of Sprycel in inhibiting BCR-ABL *in vitro* because this was but one of a number of possible mechanisms of action for Sprycel, which might explain its efficacy in imatinib resistant patients. The context of the statement did not suggest this particular mechanism of action of Sprycel should be considered in isolation to be wholly responsible for its clinical efficacy in patients with imatinib resistance. That this was the case was apparent from the layout of the text on page 5. There was a heading relating to 'mechanism of action' and then there were bullet points, including this one, which listed the possibilities.

Bristol-Myers Squibb noted that Novartis had further alleged that the claim 'Sprycel is 325 fold more potent than imatinib' implied that dasatinib had superior efficacy to imatinib and that there were no comparative benefits with respect to side-effect profile or cost.

Dasatinib had been proven, within its licensed indication, to be effective when a patient had imatinib resistance. Also, there was no cross-intolerance between imatinib and dasatinib meaning that dasatinib was a suitable treatment for patients who developed intolerance to imatinib. Bristol-Myers Squibb did not consider that cost was relevant to this allegation of a breach of Clause 7.2, but it should be noted that Sprycel was able to be used when patients developed resistance on 800mg/day of imatinib. The cost of 800mg of imatinib was more than the daily cost of Sprycel.

As above, the purpose of the claim 'Sprycel is active against all BCR-ABL mutations tested except T315I' was to inform of but one possible mechanism of action for Sprycel which might explain its efficacy in imatinib resistant patients. The context of the statement did not suggest that this particular mechanism of action of Sprycel should be considered in isolation to be wholly responsible for its clinical efficacy in patients with imatinib resistance. That this was the case was apparent from the layout of the text on page 5. There was a heading relating to 'mechanism of action' and then there were bullet points, including this one, which listed the possibilities.

Bristol-Myers Squibb denied all allegations of a breach of Clause 7.2.

PANEL RULING

The Panel noted that the leavepiece was entitled 'Sprycel Chronic phase CML For imatinib resistant or intolerant patients'. Page 2 was headed 'Sprycel in Chronic phase', and pages 2, 3 and 4 all referred at some point to imatinib resistant CML patients. It was thus in this context that page 5, headed 'Selectivity' would be read.

The Panel did not consider that, grammatically, the claim 'Sprycel has a different mechanism of action' was a hanging comparison. Further, the Panel considered that given the content of the previous pages, and the title of the leavepiece, it would be obvious to the reader that the claim compared Sprycel with imatinib. No breach of Clause 7.2 was ruled.

The Panel noted that the claim 'Sprycel also targets other oncogenic pathways such as: c-KIT, Ephrin receptor kinases, PDGF ß receptor' was referenced to the summary of product characteristics (SPC). Section 5.1 stated that dasatinib inhibited the activity of the BCR-ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases and PDGF ß receptor. The Panel noted the submission by Novartis, and the acceptance by Bristol-Myers Squibb that such pathways were implicated in malignancies other than CML. Nonetheless the claim at issue was made in a leavepiece specifically targeted at CML. Given the context in which it appeared the Panel did not consider

that the claim implied that Sprycel had clinical activity in any condition other than CML. The claim was neither misleading in that regard and nor did it promote the use of Sprycel beyond its SPC. The Panel considered that whilst the page was headed 'Selectivity' there was no actual claim that Sprycel was selective. Another page stated, beneath the heading 'Selectivity' that Sprycel offered a new multi-targeted mechanism of action. No breach of Clause 3.2 was ruled.

The Panel noted that the subheading 'Sprycel has a different mechanism of action' was asterisked to the footnote, 'Based on *in vitro* data' which appeared in small, grey typeface, at the bottom of the page. The supplementary information to Clause 7 of the Code stated that in general claims should not be qualified by the use of footnotes and the like. Further, the supplementary information to Clause 7.2 stated that data derived from, *inter alia*, *in vitro* studies should be used with care so as to not mislead as to its significance.

The Panel considered that, except for 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*', it was not clear from the outset that all other claims on page 5 regarding selectivity were based on *in vitro* data. Readers would assume that they related to the clinical situation which was not so. Bristol-Myers Squibb had not submitted any data to show the relevance of the claims to clinical practice. Bristol-Myers Squibb had submitted that the bullet points on page 5 'listed the possibilities' with regard to the product's mechanism of action. This was not entirely clear from the leavepiece. The Panel considered that, given the context in which they were made, the claims 'Sprycel is the first and only therapy to bind to both active and inactive conformations of BCR-ABL' and 'Sprycel is active against all BCR-ABL mutations tested, except T315I' were misleading as alleged; both were ruled in breach of Clause 7.2.

The Panel noted that the claim 'Sprycel is 325 fold more potent than imatinib in BCR-ABL inhibition assays *in vitro*' was not a claim for superior potency in relation to weight as alleged. Nonetheless, Bristol-Myers Squibb had not submitted any data to show what relevance this *in vitro* data had in clinical practice. The company submitted that it was one of a number of possible mechanisms of action for Sprycel which might explain its efficacy in imatinib resistant patients. The Panel did not consider this was entirely clear from the leavepiece as noted above. The clinical relevance of the data was not sufficiently clear to the reader. The Panel considered that the claim was misleading in this regard. A breach of Clause 7.2 was ruled.

Complaint received	**6 July 2007**
Case completed	**28 August 2007**

CASE AUTH/2019/7/07

LEO PHARMA v GALDERMA

Silkis 'Dear Doctor' letter

Leo Pharma complained about a Silkis Ointment (calcitriol) letter sent to GPs by Galderma following Leo's announcement of the impending discontinuation of Dovonex Ointment (calcipotriol). The letter suggested that for psoriasis patients who preferred a topical Vitamin D medicine, then Silkis might be a suitable alternative.

Leo alleged that the claim 'Silkis has demonstrated comparable efficacy to a steroid in mild to moderate psoriasis' which was referenced to Camarasa *et al* (2003) exaggerated the efficacy of Silkis compared to a steroid and implied that Silkis was similar or equivalent in efficacy to a steroid in mild to moderate psoriasis.

The Panel noted that Camarasa *et al* had compared the efficacy and duration of remission post-treatment of Silkis ointment with betamethasone dipropionate ointment in patients with chronic plaque-type psoriasis of at least moderate severity. The authors described the efficacy of the two medicines as broadly comparable; there were, however, some differences between them. Global improvement and global severity scored at treatment endpoint showed statistically significant differences in favour of betamethasone dipropionate ($p<0.05$); however the absolute reduction in psoriasis area and severity index (PASI) was comparable between the groups. A statistically significantly ($p<0.01$) higher proportion of responders remained in remission following Silkis treatment (48%) than betamethasone treatment (25%).

The Panel considered that, given the findings of Camarasa *et al*, the claim 'Silkis has demonstrated comparable efficacy to a steroid in mild to moderate psoriasis' was too broad such that it was misleading. It implied that in patients with mild to moderate psoriasis, the efficacy observed with Silkis had been shown to be statistically similar to that of a steroid which was not so. The Panel considered that the claim was misleading in this regard and could not be substantiated. Breaches of the Code were ruled.

Leo alleged that the claim 'Silkis ointment has demonstrated greater cosmetic acceptability when compared with Dovonex ointment' referenced to Marty *et al* (2005) relied on conflicting evidence and in that regard was inaccurate and misleading and could not be substantiated.

The Panel noted that Marty *et al* compared the viscosity and clinical acceptability of, *inter alia*, Silkis Ointment and Dovonex Ointment when applied to psoriatic skin. Compared to Dovonex, Silkis Ointment was statistically significantly superior in terms of fluidity and spreadability. There was no difference between the products in terms of sticky skin sensation. No statistically significant difference was shown between Silkis and Dovonex for pleasant consistency, pleasant sensation on the skin, nourishing properties and pleasant use. Regarding the overall subject preference there was no difference in preference between Silkis and Dovonex.

The Panel considered that the claim 'Silkis ointment has demonstrated greater cosmetic acceptability when compared with Dovonex ointment' was too broad given the data in Marty *et al*. Cosmetic acceptability covered a number of aspects and in most there had been no statistically significant difference between Silkis and Dovonex. The areas where Silkis had been shown to be superior to Dovonex were limited to fluidity and spreadability. The Panel considered that the claim was misleading as alleged and could not be substantiated. Breaches of the Code were ruled.

Leo alleged that the claim '…Silkis can provide a cost effective option within the Vitamin D topical market…' was inaccurate and misleading because although Silkis might cost less than competitors, it was not necessarily cost effective. The only potential substantiation that had been provided was that the cost of a 100g tube of Silkis was £16.34. This was a price not a cost-effectiveness assessment. Galderma had not, to Leo's knowledge, performed any health economic evaluation to support this claim. Galderma had undertaken to be more explicit in future promotional material by referring to the comparative costs (per gram) of the two products but this still did not justify the continued use of the term 'cost effective' in its material. Leo was concerned that Galderma did not appreciate the meaning of the term 'cost effective' and had confused 'cheap' with 'cost effective'.

Furthermore, Leo believed that Galderma was disingenuous when it maintained that Silkis might be cost effective merely by including the letter 'a' in its claim. If this was acceptable by implication, any medicine that had any effect, no matter how small, and any cost, no matter how big might be described as being cost effective.

The Panel considered that there was an element of comparison involved with a claim 'a cost effective option', even if no other product was mentioned. The claim at issue referred to the vitamin D topical market. Although Dovonex Ointment was to be discontinued Curatoderm Ointment would still be available. The claim for cost-effectiveness had been related solely to the acquisition cost of Silkis. The letter had not dealt with the economic evaluation of the effectiveness of Silkis and no data had been

provided to substantiate the claim. In the Panel's view the term 'cost effective' referred to more than just the acquisition cost of a medicine. Other factors such as relative efficacy, incidence of side effects, etc, had to be taken into account. The Panel decided that the claim 'Cost effective' was misleading and had not been substantiated and ruled breaches of the Code.

Leo Pharma complained about a 'Dear Doctor' promotional letter for Silkis Ointment (calcitriol) (ref CAL/11/0307) sent to GPs by Galderma (UK) Limited. The letter was sent following Leo's announcement of the impending discontinuation of Dovonex Ointment (calcipotriol) and suggested that for psoriasis patients who preferred a topical Vitamin D medicine, then Silkis might be a suitable alternative.

1 Claim 'Silkis has demonstrated comparable efficacy to a steroid in mild to moderate psoriasis'

This claim was referenced to Camarasa *et al* (2003).

COMPLAINT

Leo alleged that the claim exaggerated the efficacy of Silkis compared to a steroid and in that regard was inaccurate and misleading in breach of Clause 7.2 of the Code. Leo further alleged that the claim could not be substantiated in breach of Clause 7.4.

Leo submitted that the dictionary definition of 'comparable' provided two potential meanings, either 'worthy of comparison' or 'similar or equivalent'. In the context of this claim it was self-evident that the intended meaning and the meaning which all readers would infer was 'similar or equivalent'. In effect Galderma had claimed that Silkis was similar or equivalent in efficacy to a steroid in mild to moderate psoriasis.

Camarasa *et al* stated that both treatments were efficacious but that 'Global improvement and global severity scores at treatment endpoint showed statistically significant differences in favour of betamethasone dipropionate ($p<0.05$)'. In the efficacy evaluation section it was stated that 'It was noted that the proportion of patients whose psoriasis completely cleared was twice as large with betamethasone dipropionate ointment (20%) in comparison with those who cleared with Silkis ointment (9%)'. Bearing in mind that this study was supported by a grant from Galderma and hence any potential bias in describing the results was likely to lean in favour of Galderma's product, the strongest claim that the authors made in their discussion was that the active treatments were 'broadly comparable in terms of efficacy', the word 'broadly' markedly diminished the degree of similarity being described and so Leo believed that Galderma had overstated and exaggerated the findings in its claim that the efficacy of Silkis was 'comparable' to a steroid.

A literature search had revealed no alternative papers capable of substantiating this claim.

RESPONSE

Galderma submitted that the claim was for comparable efficacy, not identical or superior efficacy, which could not be substantiated. The primary efficacy variable of Camarasa *et al* was to show a difference between the treatments of at least 0.6 in global improvement score at endpoint – this was the basis of the sample size calculation. The results showed that Silkis decreased the global score by a mean of 1.58 compared with 1.36 for betamethasone. This meant that there was no significant difference between the two ointments. The authors chose a difference of 0.6 as being clinically relevant. Thus, the ointments were comparable in both statistical and clinical terms.

The following statements should be noted regarding comparable efficacy made in Camarasa *et al*:

- 'Both calcitriol 3μg/g ointment and betamethasone dipropionate 0.05% ointment were found to be efficacious. Similar proportions of patients (79% in the calcitriol group and 82% in the betamethasone group) showed definite or considerable improvement in their psoriasis, or total clearance of lesions by treatment endpoint (Table II)'.
- 'Both treatment groups showed a clinically relevant decrease in the mean global severity score which, at endpoint, was 1.58 for the calcitriol group and 1.36 for the betamethasone group ($p>0.05$). Each treatment also resulted in a marked improvement in the PASI [psoriasis area and severity index] from baseline to endpoint (Table II), with the absolute reduction in the mean PASI at endpoint being comparable between groups ($p>0.05$)'.

The authors concluded that either treatment could be used to give a good clinical response. Thus the claim accurately reflected the conclusions of Camarasa *et al*, which substantiated the claim. Galderma thus denied a breach of Clauses 7.2 and 7.4.

Galderma noted that all of the authors were leading independent clinicians and that the study was published in a respected peer-reviewed publication. Galderma questioned whether Leo, in its comments about sponsorship and authorship of Camarasa *et al*, had challenged the professional conduct of the investigators or the independence of the publication. This was particularly relevant given that at least two of the authors, Ortonne and Dubertret, had previously published several papers supporting Leo's topical vitamin D products. Indeed publications authored by these individuals were cited within Leo promotional materials.

PANEL RULING

The Panel considered that, in common parlance, if two medicines were described as comparable then prescribers and patients would generally not mind which one was used. The Code required material including comparisons to have a statistical foundation. Clinical relevance was an important consideration.

The Panel noted that Camarasa *et al* had compared the efficacy and duration of remission post-treatment of Silkis ointment with betamethasone dipropionate ointment in patients with chronic plaque-type psoriasis of at least moderate severity. The authors described the efficacy of the two medicines as broadly comparable; there were, however, some differences between them. Global improvement and global severity scored at treatment endpoint showed statistically significant differences in favour of betamethasone dipropionate ($p<0.05$); however the absolute reduction in psoriasis area and severity index (PASI) was comparable between the groups. A statistically significantly ($p<0.01$) higher proportion of responders remained in remission following Silkis treatment (48%) than betamethasone treatment (25%).

The Panel considered that, given the findings of Camarasa *et al*, the claim 'Silkis has demonstrated comparable efficacy to a steroid in mild to moderate psoriasis' was too broad such that it was misleading. It implied that in patients with mild to moderate psoriasis, the efficacy observed with Silkis had been shown to be statistically similar to that of a steroid which was not so. The Panel considered that the claim was misleading in this regard and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

2 Claim 'Silkis ointment has demonstrated greater cosmetic acceptability when compared with Dovonex ointment'

This claim was referenced to Marty *et al* (2005).

COMPLAINT

Leo alleged that the claim relied on conflicting evidence and in that regard was inaccurate and misleading in breach of Clause 7.2. Leo further alleged that the claim could not be substantiated in breach of Clause 7.4.

Leo noted that Marty *et al* suggested that Silkis was better than Dovonex in only 2 out of 7 variables, namely fluidity and spreadability, however, calcipotriol was superior in the sticky skin sensation characteristic. The authors noted that 'no statistical difference between calcitriol and its competitors was noted for: pleasant consistency, pleasant sensation on the skin, nourishing properties and pleasant use'. The claim at issue was for overall cosmetic acceptability rather than individual variables tested and in this respect, Marty *et al* stated 'there was no statistically significant difference in the aspect between Silkis and Dovonex'. Furthermore, regarding overall subject preference it was stated that 'there was no difference in preference between Silkis and Dovonex'.

Despite these fairly definitive statements Marty *et al* was then rather unclear as to how it arrived at the final statement in its discussion and conclusion that 'significant differences in the subjects' cosmetic acceptability in favour of calcitriol 3μg/g ointment compared to calcipotriol 50μg/g and tacalcitol 4μg/g ointments could be demonstrated'. Indeed, the introductory abstract stated that calcitriol and calcipotriol showed similar results to each other compared to tacalcitol whose viscoelastic parameters were 4 times higher. The authors did not provide any information on sponsorship.

Given the apparently conflicting statements and the uncertainty of the true results and conclusions to be gleaned from Marty *et al*, it would be unwise and potentially misleading to rely on this one paper in isolation to substantiate any claim of superiority in cosmetic acceptability between calcitriol and calcipotriol. No additional substantiation in support of this claim could be found.

RESPONSE

Galderma noted that Marty *et al* assessed the *in vitro* rheological properties of three vitamin D ointments and paralleled those results with an assessment of the clinical acceptability of the three ointments when applied to the skin of psoriatic subjects.

The *in vitro* rheological assessments showed that Silkis Ointment had better fluidity and flow than Dovonex which suggested that it was easier to apply to the skin.

The clinical acceptability assessment investigated primarily patients' views on fluidity, ease of spread and sticky skin sensation by questionnaire. Questions were also asked on the aspect, consistency, sensation on the skin, nourishment of the skin and the use.

The results showed that in two of the three primary assessment parameters (fluidity and ease of spread) Silkis was significantly superior to Dovonex. There was no significant difference between the two products on the third parameter, the sensation of stickiness. The supplementary questions did not reveal any further differences between the products. The authors stated that Silkis had optimal rheological characteristics for topical application to psoriatic skin and these *in vitro* results were confirmed by assessment of patient perception.

Marty *et al* concluded that 'Significant differences in the subjects' cosmetic acceptability in favour of calcitriol 3μg/g ointment compared to calcipotriol 50μg/g and tacalcitol 4μg/g ointment could be demonstrated'.

This study provided clear objective data to support the claim that Silkis had demonstrated greater cosmetic acceptability when compared to Dovonex Ointment.

Galderma denied a breach of Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that Marty *et al* compared the viscosity and clinical acceptability of, *inter alia*, Silkis Ointment and Dovonex Ointment when applied to psoriatic skin. Patients with mild to moderate psoriasis were asked to compare Silkis with Dovonex over a two day period. After each product application patients were asked about the fluidity, easiness to spread and

sticky skin. Further questions concerned the aspect [sic], consistency, sensation on the skin, nourishment of the skin and the use of each product. Compared to Dovonex, Silkis Ointment was statistically significantly superior in terms of fluidity and spreadability. There was no difference between the products in terms of sticky skin sensation. No statistically significant difference was shown between Silkis and Dovonex for pleasant consistency, pleasant sensation on the skin, nourishing properties and pleasant use. Regarding the overall subject preference there was no difference in preference between Silkis and Dovonex.

The Panel considered that the claim 'Silkis ointment has demonstrated greater cosmetic acceptability when compared with Dovonex ointment' was too broad given the data in Marty *et al*. Cosmetic acceptability covered a number of aspects and in most there had been no statistically significant difference between Silkis and Dovonex. The areas where Silkis had been shown to be superior to Dovonex were limited to fluidity and spreadability. The Panel considered that the claim was misleading as alleged and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

3 Claim '…Silkis can provide a cost effective option within the Vitamin D topical market…'

COMPLAINT

Leo alleged that the claim was inaccurate and misleading because although Silkis might cost less than competitors, it was not necessarily cost effective and so breached Clause 7.2. It also breached Clause 7.4 because it was incapable of substantiation and Clause 7.5 because on request, Galderma had failed to provide any substantiation of the claim.

The only potential substantiation that had been provided was that the cost of a 100g tube of Silkis was £16.34. This was a price not a cost-effectiveness assessment. Galderma had not, to Leo's knowledge, performed any health economic evaluation to support this claim. Galderma had undertaken to be more explicit in future promotional material by referring to the comparative costs (per gram) of the two products but this still did not justify the continued use of the term 'cost effective' in its material. Leo was concerned that Galderma did not appreciate the meaning of the term 'cost effective' and had confused 'cheap' with 'cost effective'.

Furthermore, Leo believed that Galderma was disingenuous when it maintained that Silkis might be cost effective merely by including the letter 'a' in its claim. If this was acceptable by implication, any medicine that had any effect, no matter how small, and any cost, no matter how big might be described as being cost effective. Leo believed it was inaccurate, misleading and unacceptable to make a claim of cost effectiveness for any product without reference to a comparative health economic evaluation of some sort that was relevant to the market in question.

RESPONSE

Galderma noted that the claim did not mean that Silkis had been shown to be more cost effective than any other medicine. This would indeed have been an irrelevant comparison, given that Leo was writing to health professionals announcing the imminent withdrawal of its vitamin D ointment from the UK market. Galderma used the word 'a' which clearly showed that it was aware that many factors had to be taken into account when assessing the economic worth of a medicine. Galderma could not see, from the Code, that a health economic evaluation was a prerequisite for a claim of a product being 'a cost-effective option'. Galderma accepted that if it claimed that Silkis was either the only cost effective choice or a more cost effective choice than a named therapy then data would have been needed to back this up.

Galderma denied breaches of Clauses 7.2, 7.4 and 7.5.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2 of the Code stated that care must be taken that any claim involving the economic evaluation of a medicine was borne out by the data and did not exaggerate its significance. The Panel considered that there was an element of comparison involved with the claim 'a cost effective option', even if no other product was mentioned. The claim at issue referred to the vitamin D topical market. Although Dovonex Ointment was to be discontinued Curatoderm Ointment would still be available. The claim for cost-effectiveness had been related solely to the acquisition cost of Silkis. The letter had not dealt with the economic evaluation of the effectiveness of Silkis and no data had been provided to substantiate the claim. In the Panel's view the term 'cost effective' referred to more than just the acquisition cost of a medicine. Other factors such as relative efficacy, incidence of side effects, etc, had to be taken into account. The Panel decided that the claim 'Cost effective' was misleading and had not been substantiated and ruled breaches of Clauses 7.2, 7.4 and 7.5.

Complaint received	**11 July 2007**
Case completed	**5 September 2007**

CASE AUTH/2021/7/07 and AUTH/2024/7/07

HEALTH BOARDS v LUNDBECK

Letter about Cipralex

Two health boards alleged separately that a letter about Cipralex (escitalopram), which they submitted was sent to GPs by Lundbeck, misleadingly suggested that they had endorsed the use of the product for generalised anxiety disorder. Cipralex was not recommended in their local formularies for the treatment of depression and its use in generalised anxiety disorder had not yet been considered by their drug and therapeutics committees. The letter suggested that the health boards had already endorsed Cipralex, not that this was only a proposal. Sending such correspondence to GPs was alleged to be in breach of the Code and did not encourage partnership working with the pharmaceutical industry.

The Panel noted that that the local representative had amended a certified letter and sent it to a number of health professionals. This was outside Lundbeck's instructions. The Panel considered that the letters were misleading about the health boards' positions regarding the use of Cipralex and were not capable of substantiation in that regard. Breaches of the Code were ruled in each case. The Panel considered that high standards had not been maintained and thus ruled a breach of the Code. On balance the Panel did not consider that the circumstances warranted a breach of Clause 2 which was reserved as a sign of particular censure.

Two health boards complained separately about a Cipralex (escitalopram) letter (ref 0407/ESC/342/411) which they submitted was sent to local GPs by Lundbeck Ltd.

COMPLAINT

Each health board alleged that the letter misleadingly suggested that they had endorsed the use of Cipralex for generalised anxiety disorder. Neither had had any discussion with Lundbeck regarding this issue.

Cipralex was not recommended in their local joint formularies for the treatment of depression, and its use in generalised anxiety disorder had not yet been considered by either drug and therapeutics committee.

The letter suggested that the health boards had already endorsed Cipralex, not that it had only been proposed that they endorse it.

The health boards alleged that sending such correspondence to GPs was in breach of the Code and did not encourage them to work in partnership with the pharmaceutical industry.

When writing to Lundbeck, the Authority asked it to respond in relation to Clauses 2, 7.2, 7.4 and 9.1 of the Code.

RESPONSE

Lundbeck stated that the letter in question was modified from the original certified version by one of its key account executives such that the critical first paragraph was removed and therefore was sent out as unapproved copy. The letter was sent to the intended audience (thirteen budgetary decision makers in the two local health boards) and prescribing information was attached. This was not a blanket mailing to GPs as suggested by the complainants.

The original certified letter suggested a proposition that would be potentially beneficial to both parties, regarding the use of Cipralex in generalised anxiety disorder. In the certified template, there was clear guidance on the need to state the health board's current position on the prescribing of Cipralex, which should be substantiated by seen evidence. In the template, this should be followed by Lundbeck's proposition thus removing the possibility of misinterpretation. In the case of the letters at issue, the key account executive in question removed this critical first statement.

To ensure correct use of these materials, as per Lundbeck's usual procedures, a clear brief was given to the key account executive team and their managers in May 2007. The training covered the correct use of, and audience for, the letter in question and emphasised that it could not be modified beyond filling in the details to populate the template; it was further made clear that it could only be sent to key decision makers involved in guideline development and budgetary decisions. In accordance with the Code all representative briefing material was certified, including the supporting training brief.

It was significant that both complaints had originated from the same unapproved copy used by the key account executive. No complaints had been received from a customer who received the original certified copy.

Lundbeck had immediately withdrawn the template letters from use and, within a week of receipt of the complaint, had re-trained key account executives and their managers on the Code and correct use of materials. First stage disciplinary proceedings had been initiated with the key account executive in question.

Lundbeck in no way condoned or justified the use of its unapproved copy, but re-iterated that this was an incident which ran contrary to its usual high standards and processes. To this end Lundbeck had acted immediately and decisively as outlined above.

PANEL RULING

The Panel noted that that the local representative had amended a certified letter and had sent it to a number of health professionals. This was outside Lundbeck's instructions.

The Panel considered that the letters were misleading about the health boards' positions regarding the use of Cipralex and were not capable of substantiation in that regard. Breaches of Clauses 7.2 and 7.4 were ruled in each case.

The Panel considered that high standards had not been maintained and thus ruled a breach of Clause 9.1.

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

During its consideration of this case the Panel was concerned that representatives could add what might be quite detailed information about their understanding of the use of Cipralex within the local health board to a template promotional letter without the need to have the letter separately certified. This did not appear to meet the requirements of Clause 14.1 that promotional material be certified in its final form. The Panel requested that Lundbeck be advised of its concerns in this regard.

Case AUTH/2021/7/07

Complaint received	**10 July 2007**
Case completed	**28 August 2007**

Case AUTH/2024/7/07

Complaint received	**20 July 2007**
Case completed	**28 August 2007**

CASE AUTH/2022/7/07

GENERAL PRACTITIONER v BEACON

Episenta unsolicited email

A general practitioner complained about an email relating to Episenta (prolonged release sodium valproate) which he had received from Beacon. The email was a copy of the unsolicited spam emails which he had received over the last several months. The complainant submitted that he would never have given out his email address voluntarily, or allowed somebody else to do so on his behalf in order that he should get these in the first place. Furthermore the unsubscribe function did not work.

Should the Authority be able to contact the source, the complainant would be grateful if it could explain how it got his details.

The Panel considered that the email on epilepsy was clearly promotional material for Episenta. Whilst some of it might have been written by an independent medical writer it was nonetheless an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf. The email had a link to prescribing information and the company logo appeared in the top right-hand corner of the page provided by the complainant. Beacon had paid the agency to produce the email and send it to health professionals with an interest in epilepsy. The page of the email provided by the complainant referred to prolonged release sodium valproate in general and Episenta in particular. The presentation to Beacon from the agency explained that each email comprised updates in disease area research, sponsors' treatment and an independent key opinion leader article. They were designed to complement and ultimately replace conventional mail shots. Companies paid the agency for the information to be distributed by email. The provision of such material electronically had to comply with the Code and in this case the email in question was the responsibility of Beacon.

The Panel noted that the agency operated an opt-in process for receipt of email. Some five years ago every doctor on the database was sent a questionnaire which included consent to receive a variety of email material, both educational and promotional. The Panel did not have a copy of this questionnaire. This information had been validated over the past five years. The email sent to the complainant and others, dated 27 February, informed the reader that having been verified as an NHS employee they were entitled to unrestricted access to data held on www.nhsdatabase.com. Recipients were required to register. The email then referred to an annual verification process and continued '[the agency] will from time to time send details by email about our affiliates' products and services; however please be advised that we will not share your emails with third parties'. The Panel did not consider this to be an opt-in to receive promotional material as submitted by Beacon; the nature of the material was not made clear nor did it appear that recipients were given any choice in this regard. The Panel also noted the script used for the telephone review of health professionals' details: health professionals were told that the company would, from time to time, send details by email about its affiliates' products and services relevant to the health professional's area of specialism, such as education on disease areas. The text did not make it abundantly clear that the company intended to send promotional material from pharmaceutical companies. The script did not cover the situation where the health professional declined to receive such material.

The Panel noted that a letter from the agency to Beacon stated that the opt-out function had previously been limited to a specific medical category or healthcare topic unless specifically requested. Blanket opt-out would be permitted in the future. The letter stated that the complainant 'did not request a blanket opt-out in his previous unsubscribe requests'. This was confusing as it suggested that requests to opt-out from the complainant had indeed been received whereas the complainant had thought that the opt-out facility was not working.

The Panel considered that the email had been unsolicited. There was no evidence to show that the complainant had given prior consent to receive by email promotional material from a pharmaceutical company. A breach of the Code was ruled.

A general practitioner complained about an email relating to Episenta (prolonged release sodium valproate) which he had received from Beacon Pharmaceuticals Ltd.

COMPLAINT

The complainant stated that the email was a copy of the unsolicited spam emails which he had received over the last several months. In the complainant's case, it was impossible that he would either have given out his email address voluntarily, or allowed somebody else to do so on his behalf in order that he should get these in the first place. Furthermore the unsubscribe function did not work.

Should the Authority be able to contact the source, the complainant would be grateful if it could explain how it got his details.

When writing to Beacon, the Authority asked it to respond in relation to Clause 9.9 of the Code.

RESPONSE

Beacon stated that it commissioned the agency to produce an educational email and send it to healthcare workers on

its database that might have an interest in epilepsy on 25 June. The major part of the email was written by an independent medical writer. The content of the email was not relevant to the complaint, so no further details relating to its content were provided. Beacon's target audience was stated as being neurologists, paediatricians, medical information hospital pharmacists, principal hospital pharmacists, primary care trust formulary pharmacists and interested GPs.

The complainant noted that this was one of a series of emails received from the agency. For clarification this email was Beacon's first and only activity with this company. The agency had informed Beacon that its former clients included major pharmaceutical companies.

Provided was a copy of a presentation sent to Beacon by the agency which listed former clients. Of particular importance to Beacon was the reassurance that the email conformed to ABPI guidelines in that it had a strict 'opt-in' policy. This was also emphasised in the covering sheet describing the NHS e-messaging service.

The complainant stated that he/she did not give permission for emails to be sent. This should be checked before credence was given to the complaint. Beacon raised this point with the agency and the relevant parts of its response were given below:-

> 'It is worth noting that our database on healthcare professionals has been built up over approximately 15 years with regular contact between our database research department and NHS organisations. During this time email addresses have been freely given by those who wish to receive information on a variety of topics.
>
> Some of the transmissions are from such organisations as the ……, as well as universities and pharmaceutical companies such as yourselves.
>
> In the case of the other pharmaceutical companies, I can assure you that we have a considerable amount of repeat business from them, so clearly this would indicate their satisfaction with the results.
>
> With regard to the opt-in process, some 5 years ago every doctor on our database was sent a questionnaire which when completed included a consent to receive a variety of email material, both educational and promotional, as well as newsletters, etc.
>
> Over the past 5 years we have consistently validated this information via additional questionnaires and follow up telephone calls. We currently hold data on 36,000 GPs of which c.19,500 are presently validated, so as you can imagine this is a daily ongoing process.
>
> It might be worth noting that of the hundreds of thousands of emails that have been sent in those years, less than 1% of the recipients choose to opt out, a statistic which I think speaks for itself.
>
> On the subject of whether the doctor in question did or did not give his/her email address to our researchers, or whether it was given on his behalf, this can only be resolved if we have his/her identity. Once we have that it should be possible to locate the relevant paperwork which will show who gave over the information and on what date.'

The complainant stated that the unsubscribe function did not work. The unsubscribe button could be seen at the bottom of the screen print provided by the complainant. It was difficult to comment on the complainant's observation other than saying that the unsubscribe function worked on the email sent to Beacon. The agency had told Beacon that up to 20 July, of the 3,800 doctors that opened the email, 20 requests to unsubscribe were received. As it was the same email that was sent out this suggested that there might have been an issue related to the complainant's computer.

In conclusion, before Beacon commissioned the agency, it enquired that its procedures were in line with the Code and was assured that they were. Subsequent to the complaint the agency had continued to assert that its email campaigns were from a validated opt-in database. The agency had a track record of undertaking a number of these mailing campaigns over the last few years and if this was the first complaint that had been received by the Authority, then it was difficult to malign its reputation with one isolated report.

From Beacon's point of view it was unfortunate that this complaint regarding the activities of the agency related to a Beacon campaign and had been directed at the Authority rather than Beacon. If the complaint had been directed to Beacon, it would have had the opportunity to address the issues raised directly. Indeed Beacon believed that this was still the best way of taking this matter forward.

In response to a request for further information and following permission from the complainant to disclose his identity, Beacon provided a copy of the email that was sent to the complainant earlier this year. It was in response to this email that the complainant opted-in to receive information from the agency by email. Also provided was a copy of the standard telephone script that the agency used when validating its database.

Beacon stated that it was made clear in the initial email that recipients might receive email material regarding 'affiliates products or services'. It might be true that this was not completely explicit in the wording used by the agency, but we were all used to ticking similar boxes on all sorts of forms, emails and websites. If we say yes, then we fully expect to receive promotional material. The wording was more specific in the telephone script.

The information in the email was not in the email itself, but was provided in a link to a website. If the doctor did not want to click this link then they did not have to.

The email contained information on a disease area written by an independent expert. Where it was sponsored by a pharmaceutical company then there was a separate section on product information that they could choose to click if they wished. The doctor could

read the independent educational content without ever downloading the message from the sponsor.
Beacon submitted that a key point was that doctors had to opt-in to be on the database and also they had the ability to opt-out. Beacon knew that the opt-out system had worked for other doctors, but it appeared that as a result of this complaint the agency was intending to improve the system for opt-out.

PANEL RULING

The Panel noted that Clause 9.9 prohibited the use of email for promotional purposes except with the prior permission of the recipient. The Panel considered that the email on epilepsy was clearly promotional material for Episenta. Whilst some of it might have been written by an independent medical writer it was nonetheless an established principle under the Code that pharmaceutical companies were responsible for work undertaken by third parties on their behalf.

The email had a link to prescribing information and the company logo appeared in the top right-hand corner of the page provided by the complainant. Beacon had paid the agency to produce the email and send it to health professionals with an interest in epilepsy. The page of the email provided by the complainant referred to prolonged release sodium valproate in general and Episenta in particular. The presentation to Beacon from the agency explained that each email comprised updates in disease area research, sponsors' treatment and an independent key opinion leader article. They were designed to complement and ultimately replace conventional mail shots. Companies paid the agency for the information to be distributed by email. The provision of such material electronically had to comply with the Code and in this case the email in question was the responsibility of Beacon.

The Panel noted that the agency operated an opt-in process for receipt of email. Some five years ago every doctor on the database was sent a questionnaire which included consent to receive a variety of email material, both educational and promotional. The Panel did not have a copy of this questionnaire. This information had been validated over the past five years. The email sent to the complainant and others, dated 27 February 2007, informed the reader that having been verified as an NHS employee they were entitled to unrestricted access to data held on www.nhsdatabase.com. Recipients were required to register. The email then referred to an annual verification process and continued '[the agency] will from time to time send details by email about our affiliates' products and services; however please be advised that we will not share your emails with third parties'.

The Panel did not consider this to be an opt-in to receive promotional material as submitted by Beacon; the nature of the material was not made clear nor did it appear that recipients were given any choice in this regard. The Panel also noted the script used for the telephone review of health professionals' details: health professionals were told that the company would, from time to time, send details by email about its affiliates' products and services relevant to the health professional's area of specialism, such as education on disease areas. The text did not make it abundantly clear that the company intended to send promotional material from pharmaceutical companies. The script did not cover the situation where the health professional declined to receive such material.

The Panel noted that a letter from the agency to Beacon stated that the opt-out function had previously been limited to a specific medical category or healthcare topic unless specifically requested. Blanket opt-out would be permitted in the future. The letter stated that the complainant 'did not request a blanket opt-out in his previous unsubscribe requests'. This was confusing as it suggested that requests to opt-out from the complainant had indeed been received whereas the complainant had thought that the opt-out facility was not working.

The Panel considered that the email had been unsolicited. There was no evidence to show that the complainant had given prior consent to receive by email promotional material from a pharmaceutical company. A breach of Clause 9.9 was ruled.

During its consideration of this case the Panel noted that the agency stated in its presentation that the emails conformed to all ABPI guidelines. This could not possibly be so as it would depend on the content of each email and whether the necessary prior permission had been given as required by Clause 9.9.

Complaint received	**11 July 2007**
Case completed	**28 September 2007**

CASE AUTH/2023/7/07

TEACHING PRIMARY CARE TRUST PHARMACIST v PFIZER

Champix GP Referral Aid

A pharmacist at a teaching primary care trust (PCT) complained about a Champix (varenicline) GP referral aid issued by Pfizer. The referral aid was comprised of a pad of tear-off letters which were completed by providers of a smoking cessation service including community pharmacists and other health professionals, and handed to the patient to give to their GP.

The complainant noted that the letter referred patients to their GP from the pharmacy and recommended that Champix be prescribed. The complainant did not believe that a community pharmacist would have access to the necessary clinical information needed to make this recommendation. She was particularly concerned by a section of the letter, which stated, 'In cases where the patient has epilepsy or a history of psychiatric illness, the clinical justification for recommending Champix is described below…'. This seemed a wholly inappropriate way of promoting a prescription only medicine.

The Panel noted that the GP referral letter was headed 'Smoking cessation therapy' and began by giving the patient's personal details. The letter explained that the patient was receiving a support programme from the local stop smoking service and that 'Following consultation, we recommend that in order to help them give up smoking, the therapy of choice is varenicline tartrate (Champix)'. Details of the dosage regimen were given. The GP was also advised that the patient had been encouraged to enrol in the LifeREWARDS programme (www.myliferewards.co.uk). The letter continued 'To ensure that Champix is suitable for this patient, we have already checked the following' and listed a number of clinical parameters under the headings 'Motivated to quit', 'Contraindictions' and 'Warning/precautions'. The final parameter under 'Warning/precautions' was 'Does the patient have a history of psychiatric illness?' followed by a highlighted blue box which read 'In cases where the patient has epilepsy or a history of psychiatric illness, the clinical justification for recommending Champix is described below', and was followed by space for completion by the smoking cessation adviser or health professional. Pfizer submitted that the letter was completed by smoking cessation advisers, pharmacists who provided a smoking cessation service or other health professionals.

The Panel noted that the role of smoking cessation advisers might include discussion of treatment including prescription only medicines such as Champix. Whilst the comments and recommendations made by the adviser would be relevant the Panel noted that the final prescribing decision lay with the GP.

The Panel noted the complainant's general allegation that the letter was a wholly inappropriate way of promoting a prescription only medicine. The Panel was extremely concerned about the content of the referral letter and its provision to patients. The Panel considered that the description of Champix as 'the therapy of choice' was an exaggerated claim. It implied a special merit, quality or property which could not be substantiated. A breach of the Code was ruled.

The Panel noted that the Champix summary of product characteristics (SPC) stated in the special warnings/precautions for use section that 'smoking cessation whether with or without pharmacotherapy has been associated with the exacerbation of underlying psychiatric illness (eg depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly'.

Whilst the Panel noted the role of the smoking cessation advisers it queried whether the person completing the referral form would know enough about a patient's psychiatric history to determine the clinical justification for recommending Champix. It was unclear whether they would have access to the patient's medical notes and patients might be reluctant to disclose such information.

The Panel considered that the letter would leave the patient with the unequivocal impression that Champix was the most suitable therapy and this wholly undermined the GP's ability to make a subsequent independent prescribing decision. The Panel considered that the letter clearly promoted Champix. Further a statement, 'Prescribing information for Champix can be found at the back of this document. For more information, please contact your local Pfizer representative' appeared at the bottom of the letter. It was unacceptable to provide patients with material that promoted prescription only medicines. The letter implied that the prescribing decision had already been made and that the role of the GP was to do no more than rubber stamp the recommendation to prescribe Champix. This was unacceptable. The Panel noted that the patient would already have been told about the LifeREWARDS support programme and encouraged to join it; according to the home page of the website referred to in the letter the programme was only open to those who had already been prescribed Champix.

The Panel considered that the referral letter and its provision to patients did not maintain high standards and reduced confidence in and brought discredit upon the pharmaceutical industry. Breaches of the Code, including a breach of Clause 2, were ruled.

The Panel noted its rulings above and in accordance with Paragraph 7.1 of the Constitution and Procedure decided that if there were subsequently an appeal by Pfizer it would require Pfizer to suspend use of the material pending the final outcome.

The Panel considered that the content of the letter and its provision to patients was inappropriate as described above. The undermining of the patient/GP relationship was an extremely serious matter. The Panel decided to report Pfizer to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure for it to decide whether further sanctions were warranted.

Upon appeal by Pfizer, the Appeal Board noted that smoking cessation advisers ranged from health professionals such as pharmacists and nurses to ex smokers. Although the latter could not be considered health professionals as defined in the Code they could, in certain circumstances, be considered as appropriate administrative staff. The role of smoking cessation advisers might include discussion of treatments including prescription only medicines. Whilst the comments and recommendations made by the advisers might be relevant the Appeal Board noted that the final prescribing decision lay with the prescriber such as the GP.

The Appeal Board was extremely concerned about the content and use of the referral letter. Pfizer expected health professionals to use various methods to send the referral letter to the GP without it being seen by the patient including sealing it in an envelope for the patient to deliver. This account differed from Pfizer's response to the Panel which implied that the letter was given, open, to a patient to hand to their GP. In the Appeal Board's view it was inevitable that some patients would see the letter.

The Appeal Board considered that the description of Champix as 'the therapy of choice' was an exaggerated claim. It upheld the Panel's ruling of a breach of the Code.

The Appeal Board supported the Panel's comments with regard to the smoking cessation advisor's clinical knowledge and thus their ability to recommend Champix for patients with a history of psychiatric illness. Further, the letter only referred to end stage renal disease and did not refer to moderate or severe renal impairment which according to the SPC required dose reduction.

The Appeal Board further agreed that the letter would wholly undermine the GP's ability to make an independent prescribing decision. The letter clearly promoted Champix. It was unacceptable to provide promotional material to patients about prescription only medicines.

The Appeal Board considered that advising patients that Champix was the therapy of choice and encouraging them to enrol in a support programme which was only available to Champix patients implied that the GP was to do no more than rubber stamp the recommendation to prescribe Champix; a refusal to do so would be highly likely to damage the GP/patient relationship. This was unacceptable. The Appeal Board considered that the referral letter and its provision to patients did not maintain high standards and reduced confidence in and brought discredit upon the pharmaceutical industry. The Appeal Board upheld the Panel's rulings of breaches of the Code, including a breach of Clause 2.

With regard to the Panel's report under Paragraph 8.2 of the Constitution and Procedure, the Appeal Board was concerned that as the letter was provided in the form of a tear-off pad a large number of them could still be being used. Whilst noting that the materials were no longer distributed by Pfizer the Appeal Board decided nonetheless to require Pfizer to recover the GP referral aids in accordance with Paragraph 11.3 of the Constitution and Procedure.

A pharmacist at a teaching primary care trust (PCT) complained about a Champix (varenicline) GP referral aid (ref SCE021) issued by Pfizer Limited. The referral aid was comprised of a pad of tear-off letters which were completed by providers of a smoking cessation service (smoking cessation advisers) including community pharmacists and other health professionals and handed to the patient to give to their GP.

COMPLAINT

The complainant noted that the letter referred patients to their GP from the pharmacy and recommended that Champix be prescribed.

The complainant did not believe that a community pharmacist would have access to the necessary clinical information needed to make this recommendation. She was particularly concerned by a section near the bottom of the letter, which stated, 'In cases where the patient has epilepsy or a history of psychiatric illness, the clinical justification for recommending Champix is described below…'. This seemed a wholly inappropriate way of promoting a prescription only medicine.

When writing to Pfizer, the Authority asked it to respond in relation to Clauses 2, 7.10 and 9.1 of the Code.

RESPONSE

Pfizer stated that the Champix GP referral aid was a pad of tear-off letters for use by the smoking cessation advisers, pharmacists who provided a smoking cessation service, and other health professionals during the appointment with the patient. By using the checklist provided the patient was assessed by the health professional. The tear-off letter was then given to the patient and they were advised to give it to their

GP at their next appointment. This review would help the GP when (s)he examined the patient.

This process also confirmed that the local stop smoking services had seen the patient and referred them to the GP. This ensured that the stop smoking service was being used properly, and further ensured that these patients would continue to receive the behavioural support from the service, which formed an important part of the smoking cessation treatment approach with Champix.

The complainant was particularly concerned by the section in the letter that read, 'In cases where the patient has epilepsy or a history of psychiatric illness, the clinical justification for recommending Champix is described below…'. This section was included so as to show that the smoking cessation adviser had taken the appropriate medical history, and that appropriate discussion had taken place with the patient. These were then noted on the letter so as to prompt and remind the GP that before making the final decision to prescribe or not, they should again discuss these medical conditions with the patient and then make their own clinical judgement.

The GP referral letter was intended to be used by pharmacists, smoking cessation advisers and other health professionals who were fully trained in providing such a service, and were aware of the importance of recording information about epilepsy and psychiatric conditions before recommending a specific treatment to aid their patients stop smoking. This information would then help the GP to decide, using their clinical judgement, what to do.

Pfizer considered that throughout it had behaved in an open and honest manner. It had not promoted Champix outside its marketing authorization and had complied with both the spirit and the letter of the Code. On the basis of the facts provided above, the company considered that it had not breached any clause of the Code and it was confident that its conduct had been of a high standard throughout.

PANEL RULING

The Panel noted that the GP referral letter was headed 'Smoking cessation therapy' and began by giving the patient's personal details. The letter explained that the patient was receiving a support programme from the local stop smoking service and that 'Following consultation, we recommend that in order to help them give up smoking, the therapy of choice is varenicline tartrate (Champix)'. Details of the dosage regimen were given. The GP was also advised that the smoking cessation adviser or health professional had 'encouraged this patient to enrol in the LifeREWARDS programme (www.myliferewards.co.uk)'. The letter continued 'To ensure that Champix is suitable for this patient, we have already checked the following' and listed a number of clinical parameters under the headings 'Motivated to quit', 'Contraindictions' and 'Warning/precautions'. The final parameter under 'Warning/precautions' was 'Does the patient have a history of psychiatric illness?' followed by a highlighted blue box which read 'In cases where the patient has epilepsy or a history of psychiatric illness, the clinical justification for recommending Champix is described below', and was followed by space for completion by the smoking cessation adviser or health professional. The Panel noted that the referral letter was handed to the patient to provide to his/her GP.

Pfizer explained that the letter was completed by smoking cessation advisers, pharmacists who provided a smoking cessation service or other health professionals. The Panel noted that the role of smoking cessation advisers might include discussion of treatment including prescription only medicines such as Champix. Whilst the comments and recommendations made by the smoking cessation advisers would be relevant the Panel noted that the final prescribing decision lay with the GP.

The Panel noted the complainant's general allegation that the letter was a wholly inappropriate way of promoting a prescription only medicine. The Panel was extremely concerned about the content of the referral letter and its provision to patients for them to hand to their GP.

The Panel considered that the description of Champix as 'the therapy of choice' was an exaggerated claim. It implied a special merit, quality or property which could not be substantiated. A breach of Clause 7.10 was ruled.

The Panel noted that Section 4.4 of the Champix summary of product characteristics (SPC), special warnings and precautions for use, stated that 'smoking cessation whether with or without pharmacotherapy has been associated with the exacerbation of underlying psychiatric illness (eg depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly'.

Whilst the Panel noted the role of the smoking cessation advisers it queried whether the person completing the referral form would have access to sufficient information about a patient's psychiatric history to determine the clinical justification for recommending Champix. It was unclear whether they would have access to the patient's medical notes and patients might well be reluctant to disclose such information.

The Panel considered that the letter would leave the patient with the unequivocal impression that Champix was the most suitable therapy and this wholly undermined the ability of the GP to make a subsequent independent prescribing decision. The Panel considered that the letter clearly promoted Champix. Further a statement, 'Prescribing information for Champix can be found at the back of this document. For more information, please contact your local Pfizer representative' appeared at the bottom of the letter. It was unacceptable to provide promotional material to patients about prescription only medicines. The letter gave the impression to patients that the prescribing decision had already been made and that was not

necessarily so. The overall tone implied that the role of the GP was to do no more than rubber stamp the recommendation to prescribe Champix. This was unacceptable. The Panel noted that the patient would already have been told about the LifeREWARDS support programme and encouraged to join it; according to the home page of the website referred to in the letter the programme was only open to those who had already been prescribed Champix. The Panel considered that the referral letter and its provision to patients did not maintain high standards and reduced confidence in and brought discredit upon the pharmaceutical industry. Breaches of Clauses 2 and 9.1 were ruled.

The Panel noted its rulings above and in accordance with Paragraph 7.1 of the Constitution and Procedure decided that if there were subsequently an appeal by Pfizer it would require Pfizer to suspend use of the document pending the final outcome.

The Panel considered that the content of the letter and its provision to patients was inappropriate as described above. The undermining of the patient/GP relationship was an extremely serious matter. The Panel decided to report Pfizer to the Code of Practice Appeal Board in accordance with Paragraph 8.2 of the Constitution and Procedure for it to decide whether further sanctions were warranted.

APPEAL BY PFIZER

Pfizer stated that in November 2006, the GP referral aid was pre-vetted by the Medicines and Healthcare products Regulatory Agency (MHRA) prior to the launch of Champix in December 2006. The objective of the item was outlined as it was intended to be used – 'a letter to recommend patients for Champix on a named patient basis from non-prescribers to ensure they are suitable for treatment'. After reviewing the referral aid, the MHRA did not object to its use.

The GP referral aid was a pad of tear-off letters for use by health professionals specifically where they wished to recommend a Champix prescription for a particular patient, after discussion with that patient and consideration of all available treatment options.

Stop smoking services were provided via a variety of routes including NHS local stop smoking services via pharmacies that had set themselves up to provide a stop smoking service to the community, and at GP practices often by trained nurses. Regardless of the route that the patient followed after consultation they were usually recommended a course of action that might include pharmacological therapy along with behavioural support. The recommended therapy might include a prescription only medicine (such as Champix), or nicotine replacement therapy which was available with or without prescription. As the majority of smoking cessation advisers (with the exception of some nurse and independent prescribers) were unable to prescribe medicines, they in turn referred patients to a GP who would then evaluate them, the suitability of any recommended treatment and make any relevant prescribing decision. If the adviser had prescribing powers, they could simply prescribe the chosen treatment.

Pfizer submitted that as the route to a prescription in smoking cessation was more complex than most other therapy areas, the smoking cessation advisers used referral letters such as the GP referral aid at issue to aid this process; the letters were meant to be used after the patient and adviser had discussed all treatment options. If it was decided that Champix was the best option for that particular patient then the adviser would use the referral aid in order to record important information that would aid the GP to make the final prescribing decision. It was designed to ensure that the health professional was prompted to consider important contraindications and special precautions/warnings for Champix to help ensure appropriate prescribing. As from previous experience with other oral smoking cessation therapies it was important to ensure that a complete history of epilepsy and psychiatric history was recorded as either of these conditions might be exacerbated either by the therapy itself or by the effects of stopping smoking. As 'epilepsy' and 'history of psychiatric illness', were listed as warning/precautions to the use of Champix, the referral aid had a highlighted box to ensure that the smoking cessation adviser documented any important information gathered from the patient consultation that would help the GP make the ultimate prescribing decision.

As the GP referral aid referred to Champix by name stating its indication and dosage, Pfizer considered it to be a promotional item and therefore included the prescribing information as required by Clause 4.1. Smoking cessation advisers, like other health professionals, used various routes for sharing confidential patient information with other health professionals, such as email/post/fax or delivery of sealed envelopes via the patient. It was not Pfizer's responsibility to tell health professionals how to enter into such confidential dialogue. Pfizer expected good professional practice to be maintained at all times.

The GP referral aid could be used as a tool by health professionals who were providing a smoking cessation service after they had completed their consultation with the patient and considered all relevant therapies. If Champix was then considered as a treatment option the referral aid then acted as an aide memoire by highlighting key questions and special precautions/warnings relating to Champix.

With regard to the Panel's query about whether the person completing the GP referral aid would have access to sufficient information about a patient's psychiatric history to determine the clinical justification for recommending Champix, and that a patient's medical notes might not be accessible or that patients might be reluctant to disclose such information, Pfizer submitted that stop smoking services were an integral part of the UK health system to provide patients with information about the support available to help them stop smoking. Smoking cessation advisers were health professionals who were generally considered to be experts in their line of work. Patients were often

referred to them by GPs for expert smoking cessation advice, support, and information about treatment options. The smoking cessation advisers evaluated the best treatment for their patients on a case by case basis. For some treatments patients might be passed back to their GP with a recommended treatment (which might include both non-prescription and prescription medicines). The GP then evaluated this assessment, and normally prescribed as appropriate following consultation with the patient. Specifically highlighting potential areas warnings/precautions such as epilepsy or a history of psychiatric illness, alerted the prescriber to the fact that Champix might be unsuitable for a particular patient. The GP referral aid supported the rational and clinically appropriate use of Champix.

Only where the smoking cessation adviser believed a Champix recommendation was appropriate, would the referral letter go to the GP for consideration. Pfizer did not expect any referral aids to be seen by patients, and it would never encourage or endorse this. Smoking cessation advisers, like other health professionals, used various routes for the careful exchange of confidential information with other health professionals, such as email/post/fax/sealed envelope via the patient. This was supported by various PCT guidance documents as to how referrals should be sent (examples were provided). Although not specific to smoking cessation, the guidance stipulated that referral letters handed to patients should be in sealed envelopes. Pfizer had no reason to believe that this process was not followed by smoking cessation advisers, and therefore submitted that patients would not possibly see a copy of the referral aid in question

Pfizer acknowledged that it could have been clearer on this issue in its response when it stated that the GP referral aid was handed to the patient after its completion by a health professional. However, Pfizer had no reason to believe that the health professional would not use standard practice and therefore fully expected the letter to be sealed in an envelope before being handed to the patient (if it was not sent directly to the patient's GP).

It was common practice for stop smoking services to discuss with patients the types of therapies available to help them to stop smoking. During these discussions the main objective was to evaluate what would be the best treatment option for that particular patient. When both the patient and adviser agreed on a certain treatment then that was considered the 'therapy of choice' for that particular patient and it was for these reasons that the term 'therapy of choice' was included in the referral aid; it did not imply a special merit, quality or property as noted by the Panel.

As previously stated, the main objective of the discussions between the patient and the smoking cessation adviser was to evaluate what would be the best treatment option and support programme for that particular patient. The patient would normally be told that the decision to prescribe certain treatments, such as Champix, rested with the GP. The referral aid did not state that the GP must prescribe Champix nor did Pfizer believe that the smoking cessation advisers advocated this. GPs received referral letters from many health professionals other than smoking cessation advisers, in which recommendations were made regarding treatment, but the final decision to act upon the recommendation rested with the GP who would consider other important factors from the patient's history and medical notes and prescribe the medicine considered to be the most appropriate for that patient.

Pfizer noted the Panel's concerns about the reference to the LifeREWARDS programme in the referral aid. LifeREWARDS was a personalized behavioural support programme created by Pfizer and was available only to Champix patients. Similar support programmes were offered by other companies providing smoking cessation products. All treatment options along with associated behavioural support programmes were evaluated and discussed with the patient. When Champix was recommended as a treatment option then the advisers would discuss the associated LifeREWARDS support programme with the patient as an optional form of behavioural support.

Pfizer noted that as detailed in Section 1 of the National Institute for Health and Clinical Excellence (NICE) guidance for Champix, the second recommendation stated that 'varenicline should normally be prescribed only as part of a programme of behavioural support'. The NICE guidance further elaborated in Section 4.4 that 'varenicline should normally only be provided in conjunction with counselling and support, but that if such support is refused or is not available, this should not preclude treatment with varenicline'. Pfizer submitted that it was important that smoking cessation advisers knew about LifeREWARDS as an additional help and support for patients trying to stop smoking. The odds of successfully quitting increased if the patient had access to a behavioural support programme along with pharmacological treatment (Coleman *et al* 2004). Discussing LifeREWARDS with the patient at this early stage helped ensure that they knew about the full treatment package available with Champix. The LifeREWARDS support programme was an optional behavioural modification programme that complimented the support that was provided by the stop smoking advisers.

Pfizer submitted that after the completion of the referral aid the smoking cessation advisers should inform patients that it was only a recommendation and that the GP would always have the final decision. The referral aid was not for the patient to see or read but a document that was sent from one health professional to another. The GP would then decide after taking into consideration all related aspects whether to agree with the recommendation or to choose an alternate course of action. This did not imply that patients would demand Champix, and it did not undermine the patient/GP relationship for reasons mentioned above.

In conclusion, Pfizer submitted that it had not breached Clauses 2, 7.10 or 9.1 and it was confident that its conduct, which was open and honest, had been of a high standard throughout. Pfizer submitted that it had complied with both the spirit and the letter of the Code.

COMMENTS FROM THE COMPLAINANT

The complainant disputed Pfizer's submission that smoking cessation advisers were health professionals. Many did not have a health qualification, although they would have had some specific training in smoking cessation. Even if health professionals completed the form (as would be the case with community pharmacists) they still would not have had access to the patient's medical records and would therefore not confidently know whether the patient had a history of psychiatric illness. How likely would a patient be to disclose this information? The form would be slightly more acceptable if it stated, 'Please check that this patient does not have a history of psychiatric illness or epilepsy before prescribing'. The fact that it actually stated, 'In cases where the patient has epilepsy or a history of psychiatric illness, the clinical justification for recommending Champix is described below' made this a completely different scenario. The complainant could not imagine what sort of justification a pharmacist (or even more worryingly a smoking cessation adviser who was not a health professional) would give. Where would the clinical liability lie if a GP prescribed based on this recommendation?

The complainant considered Pfizer to be rather naïve when it stated that it did not expect any referral aids to be seen by patients, and that it did not believe that patients would possibly see a copy of the referral aid. If the smoking cessation adviser or pharmacist was to obtain information about psychiatric illness, epilepsy, breast feeding, renal disease etc and was seen to be completing a form, then the patient would know what this was for and would know that the GP was being asked to prescribe Champix.

Pfizer quoted guidance from another PCT regarding how referrals should be sent ie in a sealed envelope. The complainant alleged that this guidance was not related to smoking cessation services or to community pharmacy and applied to GP referral letters to secondary care, which was an entirely different situation. If a random selection of community pharmacists were asked what they would do with the referral form it was likely that they would just hand it to the patient. There was nothing on the form to suggest otherwise.

The complainant noted that Pfizer appealed on the basis that, in cases when both the patient and adviser agreed to certain treatment, then it submitted that this was considered the 'therapy of choice'. In the absence of a prescriber during the consultation, the complainant alleged that a decision could not be made that this was the therapy of choice. A more appropriate form of wording might have been that Champix was 'a suitable option' or similar.

The complainant noted the Panel had considered that the letter implied that the prescribing decision had already been made. Pfizer had disputed this, insisting that the patient would understand that the final decision rested with the GP. Given that the patient had to give full medical details to the pharmacist or smoking cession adviser, the complainant alleged that the patient was very likely to assume that the GP would prescribe. This undermined the GP's ability to make a subsequent independent prescribing decision and undermined the relationship between the patient, the GP and the pharmacist.

The complainant noted that Pfizer's appeal seemed to rest upon extolling the values of LifeREWARDS, although this was not actually disputed in the complaint. The Panel had noted that LifeREWARDS was only open to those already prescribed Champix and that it was therefore inappropriate for it to be mentioned before prescribing had occurred. The complainant stated that the mention of LifeREWARDS at this stage actually reinforced the impression that the GP was expected to rubber stamp the decision to prescribe Champix.

The complainant noted that the Panel had considered that the GP would not have any other choice as the patient would demand Champix and this would undermine the patient/GP relationship. The complainant noted Pfizer's appeal was on the basis that the patient would not have seen the referral, would understand that this was only a recommendation and that the final decision rested with the GP. For all the reasons above, the complainant did not consider this to be an accurate reflection of what would happen.

The GP would be in a very difficult situation if they decided not to prescribe. Champix carried a black triangle status and some GPs might consider that it was not in the best interests of the patient to prescribe, which was their clinical right. However, this would cause tension between the GP and the patient, who already had a high expectation that Champix would be prescribed. It was also likely to cause tension between GPs and local community pharmacists if referrals were made using this form.

In conclusion, the complainant alleged that Pfizer had acted in breach of Clauses 2, 7.10 and 9.1 as ruled by the Panel. The complainant found nothing in Pfizer's appeal to alter the facts and change her view.

APPEAL BOARD RULING

The Appeal Board noted that the referral letters were to be completed by smoking cessation advisers. The advisers ranged from health professionals such as pharmacists and nurses to previous smokers who had stopped smoking. Although the latter could not be considered health professionals as defined in Clause 1.4 they could, in certain circumstances, be considered as appropriate administrative staff (Clause 1.1). The role of smoking cessation advisers might well include discussion of treatments including prescription only medicines such as Champix. Whilst the comments and recommendations made by the smoking cessation advisers might be relevant the Appeal Board noted that the final prescribing decision lay with the prescriber such as the GP.

The Appeal Board was extremely concerned about the content and use of the referral letter. Pfizer expected

health professionals to use various methods to send the referral letter to the GP without it being seen by the patient including sealing it in an envelope for the patient to deliver. This account differed from Pfizer's response to the Panel which implied that the letter was given, open, to a patient to hand to their GP. In the Appeal Board's view it was inevitable that some patients would see the letter.

The Appeal Board considered that the description of Champix as 'the therapy of choice' was an exaggerated claim. It implied a special merit, quality or property which could not be substantiated. A breach of Clause 7.10 was ruled. The appeal on this point was unsuccessful.

Section 4.4 of the Champix SPC, special warnings and precautions for use, stated that 'smoking cessation whether with or without pharmacotherapy has been associated with the exacerbation of underlying psychiatric illness (eg depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly'.

Whilst the Appeal Board noted the role of smoking cessation advisers it queried whether those completing the referral form would have access to sufficient information about a patient's psychiatric history to determine the clinical justification for recommending Champix. It was unclear whether they would have access to the patient's medical notes and patients might well be reluctant to disclose such information. Further, the letter only referred to end stage renal disease and did not refer to moderate or severe renal impairment which according to the SPC required dose reduction.

The Appeal Board considered that the completion of the letter by the smoking cessation adviser would give the patient the unequivocal impression that Champix was the most suitable therapy and wholly undermine the GP's ability to make a subsequent independent prescribing decision. The letter clearly promoted Champix. It was unacceptable to provide promotional material to patients about prescription only medicines.

The Appeal Board considered that advising patients that Champix was the therapy of choice and encouraging them to enrol in the LifeREWARDS support programme (which was only available to Champix patients) implied that the role of the GP was to do no more than rubber stamp the recommendation to prescribe Champix. If the GP then refused to prescribe Champix this would be highly likely to damage the GP/patient relationship. This was unacceptable. The Appeal Board considered that the referral letter and its provision to patients did not maintain high standards and reduced confidence in and brought discredit upon the pharmaceutical industry. The Appeal Board upheld the Panel's rulings of breaches of Clauses 2, and 9.1. The appeal was unsuccessful.

With regard to the Panel's report under Paragraph 8.2 of the Constitution and Procedure, the Appeal Board was concerned that as the letter was provided in the form of a tear-off pad a large number of them could still be being used. Whilst noting that the materials were no longer distributed by Pfizer the Appeal Board decided nonetheless to require Pfizer to take steps to recover the GP referral aids in accordance with Paragraph 11.3 of the Constitution and Procedure.

Complaint received	**18 July 2007**
Case completed	**18 October 2007**

CASE AUTH/2025/7/07

GENERAL PRACTITIONER v NAPP

Conduct of representative

A general practitioner complained about the promotion of BuTrans (buprenorphine transdermal patches) by a Napp representative. The duty manager of an old people's home had asked the complainant to prescribe the product. It transpired that the representative had visited the home to promote a prescription only medicine; she had also left promotional leaflets and her business card with the duty manager.

The Panel noted that the establishment visited by the representative was staffed by social workers; such employees could be considered appropriate administrative staff, or as they administered medicines, they might even come within the definition in the Code of a health professional. They were not members of the public in that regard and thus the Panel ruled no breach of the Code. However these staff were not legally entitled to choose which medicine was prescribed; they administered medicines on behalf of the prescriber. In that regard the Panel considered that the information directed at such people would be different to that used with prescribers. The Panel did not consider that the leavepiece used with the staff at the home had been tailored to their needs; Napp had submitted that it was intended for GPs and nurses. The leavepiece was not tailored to the needs of non-medical staff who only administered medicines. BuTrans was a low dose, strong opioid preparation which should only be prescribed once a patient's previous opioid history and their current general condition and medical status had been considered. An anti-emetic was recommended for the first 7 days of BuTrans patch use. The Panel queried whether the staff at the home would have sufficient clinical knowledge to understand the implications of recommending BuTrans. The Panel considered that the representative had used a piece of promotional material with an audience for whom it had not been intended. High standards had not been maintained. Breaches of the Code were ruled.

The Panel did not consider that the home was a patient organisation ie advocacy group, as referred to in the Code and no breach of the Code was ruled.

Although very concerned about the promotion of a prescription only medicine to non-medical staff in this case, the Panel, on balance, considered that Napp's actions were not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. The final decision about what, if anything, to prescribe would always lie with the prescriber. No breach of Clause 2 was ruled.

A general practitioner complained about the promotion of BuTrans (buprenorphine transdermal patches) by a representative of Napp Pharmaceuticals Limited.

COMPLAINT

The complainant stated that the duty manager old people's home in Scotland, recently asked her to prescribe BuTrans (buprenorphine) transdermal patches for some of its patients. It transpired that the representative in question had visited the home three or four times to promote a prescription only medicine; she had also left promotional leaflets and her business card with the duty manager.

The complainant alleged a breach of Clause 20.1 of the Code which stated that prescription only medicines must not be advertised to the public and Clause 20.3 which stated that information must be presented in a factual and balanced way and must not be designed to encourage patients to ask their health professional to prescribe a specific medicine.

BuTrans transdermal patches were not on the local formulary and were also not recommended by the Scottish Medicines Consortium (SMC).

It might be that the representative was unaware that she was only permitted to promote her products to health professionals and NHS managers but the complainant would be grateful if the matter could be investigated to ensure that this did not become a recurring problem.

When writing to Napp, the Authority asked it to respond in relation to Clauses 2, 9.1 and 15.2 of the Code in addition to Clauses 20.1 and 20.3 as cited by the complainant.

RESPONSE

Napp explained that the representative had visited the nursing home five times since February 2007 but had not seen the same health professionals each time. Two of these visits were solicited and three were unsolicited, but one of the unsolicited visits did not result in a completed call as no customers were available. She had no contact with the nursing home prior to February 2007.

The representative had arranged to meet the duty manager in February. However upon arrival she was told that the manager was unavailable and was asked to speak to a person whom she understood to be the Nurse in Charge, The representative gave a brief overview of BuTrans transdermal patches whereupon the Nurse in Charge thought that her staff would be interested in the product and asked the representative to return in May to give a presentation to a group of her staff.

When the representative duly arrived to give the presentation she was told that there had been an error with dates and staff availability and she was asked to return to meet nursing staff on later that month. Although she had a brief discussion about BuTrans patches with the duty manager and the Nurse in Charge the main presentation was deferred.

When, later in the month the representative presented information on BuTrans patches to a group of nurses at the home the meeting took place in a staff room out of earshot of patients, and the duty manager was not present. The representative demonstrated the use of a placebo patch and left some leavepieces (ref UK/BU-06081). The staff were very positive about the product and the representative was asked to follow up with the nursing home in the future.

In June, the representative called on the nursing home to see the Nurse in Charge who was unavailable. She left without discussing any products. In July the representative called again, but the Nurse in Charge was unavailable. A nurse who had not attended the meeting in May mentioned BuTrans patches and that he had heard about its potential benefits from his colleagues.

Napp emphasised that there had been no direct contact between the representative and any patient at this nursing home and her visits were conducted in a private room out of patients' earshot. Napp therefore assumed that the complainant was referring to discussions that took place with the duty manager.

Clause 1.1 clearly allowed medicines to be promoted to 'appropriate administrative staff' provided that all other provisions of the Code were met. Napp therefore maintained that it was entirely appropriate for the representative to give some very limited information about the product to the duty manager, so that he could make a judgment as to whether it would be appropriate to allow her to speak to his nursing staff. During the representatives' only brief discussion about BuTrans patches with the duty manager, in early May, the nursing home's Nurse in Charge was also present.

Clause 12.1 stated that promotional material should only be sent or distributed to those with a reasonable interest and that such material should be tailored to the audience. The leavepiece in question was intended for nurses and GPs and therefore the representative only left these with the nursing staff.

The complainant quoted the supplementary information to Clause 20 with reference to the fact that information should be presented in a factual and balanced way and not be designed to encourage patients to ask a health professional to prescribe a specific medicine. As far as Napp could tell from her letter, the complainant was contacted by the duty manager and not a patient. Thus there would appear to be no evidence at all that this provision had not been met.

On these grounds Napp strongly maintained that no breach of Clause 20 had occurred.

Napp acknowledged that BuTrans had not been approved by the SMC and was not on the local formulary. However the Code, and indeed UK legislation, did not restrict the rights of a pharmaceutical company to promote a product under such circumstances.

Napp continued to promote BuTrans in such circumstances in the belief that the rights of the health professional to decide what was best for the individual patient should be preserved.

Promoting a product that had been granted a marketing authorization by the Medicines and Healthcare products Regulatory Agency, but which had not been included on a particular formulary or recommended by the SMC, did not constitute a breach of the Code.

Napp believed that its representative had complied with the Code in all of her dealings with this nursing home. In particular she had conducted her discussions only with health professionals and appropriate administrative staff in suitably private locations. She had not exceeded allowable call rates and had used only certified materials which had been left with the intended and appropriate customers.

Napp therefore believed that she had maintained high standards of conduct in compliance with the requirements of Clauses 9.1 and 15.2, and furthermore that there were no grounds to suggest that Clause 2 had been breached.

In response to a request for further information Napp confirmed that the establishment visited by its representative was a care home for the elderly. Since the rules for promotion in care homes and nursing homes were identical as they related to the Code, Napp did not distinguish internally between them. The company used the terms synonymously.

Napp noted that the Code applied to 'health professionals and to appropriate administrative staff'. As defined in Clause 1.4 'health professional' included 'any other persons who in the course of their professional activities may prescribe, supply or administer a medicine'. Napp thus understood that staff working at a care home who administered medicines as part of their work were acting as health professionals rather than members of the public. The company submitted that the duty manager was appropriate administrative staff.

Care staff at the home did not wear uniforms.

Napp confirmed that its representative had asked the duty manager if she could speak to the Nurse in Charge and was directed to a named individual. At no time did the representative promote medicines to the patients (ie the public).

The Nurse in Charge was not a qualified nurse although at all times she was held out as the Nurse in Charge. At no time did she or anyone else state that she was not a qualified nurse. She had a social work

qualification and was the assistant manager of the home. As noted below, however, she was properly classed as a health professional.

Napp provided a list of the attendees to the meeting in May 2007; five were social care workers and three were social care assistants. The attendees were all selected by the Nurse in Charge as suitable and appropriate members of her staff to attend this meeting; the representative had no reason to believe otherwise.

Under the Medicines Act 1968 anyone, including social care workers and assistants in care homes could legally administer medicines to patients. Napp submitted that this qualified them as health professionals as defined by the Code.

The duty manager was not a qualified nurse but was a social worker by training. His duties and responsibilities within that role required him to have knowledge and awareness of the products being held at, administered and used at the home as well as their potential side effects. Napp submitted this qualified him as appropriate administrative staff as defined by the Code.

Napp submitted that its representative always intended to uphold high standards and that she had not promoted to the public as alleged.

PANEL RULING

The Panel noted that the Code applied to, *inter alia*, the promotion of medicines to members of the UK health professions and to appropriate administrative staff. The term 'health professional' included members of the medical, dental, pharmacy and nursing professions and any other persons who in the course of their professional activities might prescribe, supply or administer a medicine (Clause 1.4 referred).

The Panel was concerned that at the outset, Napp had not given a clear description of the establishment visited by the representative. Although the company submitted that the terms 'care home' and 'nursing home' were synonymous, in the Panel's view there was an important difference between the two – nursing homes would employ professionally qualified nurses whereas care homes would not necessarily do so. The Panel did not accept Napp's submission that the rules for promotion in care homes and nursing homes were identical as they related to the Code. The establishment visited by the representative was a care home and although it was staffed by social workers, Napp had initially referred to them as nursing staff and health professionals. This was not helpful. Napp's second response gave more information.

The Panel noted that the social workers at the care home could be considered appropriate administrative staff, or as they administered medicines they might even come within the definition in the Code of a health professional. They were not members of the public in that regard and thus the Panel ruled no breach of Clause 20.1. However these staff were not legally entitled to choose which medicine was prescribed; they administered medicines on behalf of the prescriber. In that regard the Panel considered that the information directed at such people would be different to that used with prescribers. The supplementary information to Clause 12.1 required promotional material to be tailored to the needs of the audience. The Panel did not consider that the leavepiece used with the staff at the care home had been tailored to their needs; Napp had submitted that it was intended for GPs and nurses. The leavepiece was not tailored to the needs of non-medical staff who only administered medicines. BuTrans was a low dose, strong opioid preparation for the treatment of severe opioid responsive pain conditions which did not adequately respond to non-opioid analgesics. The patient's previous opioid history and their current general condition and medical status should be considered. The leavepiece stated that an anti-emetic was recommended for the first 7 days of BuTrans patch use. The Panel queried whether the staff at the care home would have sufficient knowledge about patients' previous medical history, current medical status or anti-emetic prescribing to be able to understand the clinical implications of recommending BuTrans. The Panel considered that the representative had used a piece of promotional material with an audience for whom it had not been intended. In that regard the Panel considered that high standards had not been maintained. Breaches of Clause 9.1 and 15.2 were ruled.

The Panel did not consider that the care home was a patient organisation ie advocacy group, as referred to in Clause 20.3 and cited by the complainant. No breach of that clause was ruled.

Although very concerned about the promotion of a prescription only medicine (CD (Sch3)) to non-medical staff in this case, the Panel, on balance, considered that Napp's actions were not such as to bring discredit upon or reduce confidence in the pharmaceutical industry. The final decision about what, if anything, to prescribe would always lie with the prescriber. No breach of Clause 2 was ruled.

Complaint received	**23 July 2007**
Case completed	**7 September 2007**

MEMBER OF THE PUBLIC v GLAXOSMITHKLINE

Conduct of representative

A member of the public complained about the conduct of a representative from GlaxoSmithKline. The complainant alleged that a close friend had recently ended up hospitalized because he overdosed on medicines purchased privately from one of GlaxoSmithKline's representatives.

The Panel noted that GlaxoSmithKline's policy was to post samples to health professionals. Representatives were not allowed to hold supplies of samples for distribution. Representatives were allocated one demonstration pack per product which was actual stock overlabelled 'For demonstration purposes only. NOT for clinical use or to be left with customers'. Such packs could not be replaced unless there was a very good reason.

GlaxoSmithKline provided details of a recent audit of the representative's samples which tallied the quantity of samples requested with that ordered, despatched, returned and indicated that the request form had been checked. On the evidence before it the Panel considered that GlaxoSmithKline had an adequate system of control and accountability for samples and medicines. There was no evidence that samples had been provided to a non-health professional as alleged nor without a signed dated written request. The Panel did not consider that either the representative or the company had failed to maintain high standards. Thus no breaches of the Code including Clause 2 were ruled.

A member of the public complained about the conduct of a representative from GlaxoSmithKline UK Ltd.

COMPLAINT

The complainant stated that she was extremely upset and disgusted with GlaxoSmithKline and would have thought that a company on such a grand scale would keep its representatives inline with ABPI regulations and conduct in that they were largely trained to recognize how dangerous it was to sell samples to vulnerable individuals to line their own pockets. The complainant alleged that a very close friend had recently ended up hospitalized because he overdosed on medicines which were not prescribed by his general practitioner, in fact he had been purchasing the medicines privately for some time, now from one of GlaxoSmithKline's representatives. The complainant and the hospitalized person's family knew that he was as much to blame for the overdose as the irresponsible representative with unethical conduct, but at the end of the day if the representative had not been selling these medicines to vulnerable individuals, the complainant dreaded to think how many others would not be in such a disastrous state. The complainant was strongly considering bringing this matter to the attention of the police pending the recovery of their friend's health and in the meantime brought this matter to attention of the Authority. The complainant hoped the Authority would take this matter seriously and would bring in stringent checks on ensuring representatives maintained an ethical conduct as well as working with GlaxoSmithKline to basically tighten up their accountability of where and whom its medicine samples were littered to by its sales force - hopefully not the vulnerable members of the public.

When writing to the GlaxoSmithKline the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2, 17.1, 17.3 and 17.9 of the Code.

RESPONSE

GlaxoSmithKline submitted that it took the allegations extremely seriously and on receipt of this complaint instigated an urgent investigation.

The representative had worked for GlaxoSmithKline for a number of years on a number of products including Levitra (vardenifil), Avodart (dutasteride) and Seretide (salmeterol/fluticasone). Recently the representatives had worked in a respiratory team.

GlaxoSmithKline submitted that the during the last 12 months the representative had only requested Incheck devices (a tool for measuring effectiveness of patient inhaler technique) and placebo inhalers. The representative had no access to any other GlaxoSmithKline medicines samples and had not requested nor distributed any samples other than those detailed. Full details of these samples and the signed request forms were provided.

As per legal requirements and the Code, both of which were reinforced by GlaxoSmithKline's Stay Safe Sheet guidance, samples were only provided to customers on receipt of a written and signed request. The request was validated against three key criteria:

- Orders must only be made to a doctor whose name and address was on the request form, as defined on GlaxoSmithKline's Triton system.
- Doctors could not receive more than ten samples of a specific formulation and dose type in any 12 month rolling period.
- The sampling initiative must be active and have an end date after which no further requests would be accepted.

GlaxoSmithKline did not allow its representatives to hold samples. All samples were dispatched directly to the health practitioner as detailed in the standard operating procedure (SOP) provided. One

demonstration pack was allocated per representative and this was solely for the representative's use during a call and was not to be left with customers.

GlaxoSmithKline also required random weekly audits of representatives' sample logs. The representative in question underwent a previous successful audit of her samples 18 months ago.

The representative was understandably shocked by the seriousness of the allegations which were vigorously refuted. GlaxoSmithKline could find no evidence to support any of the allegations and, based on the company's own sample records, supported the denials of any wrongdoing. Furthermore GlaxoSmithKline submitted that its robust process maintained control and accountability of medicines held by representatives in accordance with Clause 17.9 and the company thus strongly refuted breaches of Clauses 2, 9.1, 15.2, 17.1, 17.3 and 17.9 as alleged.

As requested GlaxoSmithKline provided:

- Details of all samples provided and distributed by the representative in the last 12 months
- Copies of signed sample request forms over the same period
- Representative's Sample Audit form for the representative
- UKMED/SOP/0026 - GlaxoSmithKline UK process for the management of Samples, Placebos and Devices
- Stay Safe Sheet 31 GlaxoSmithKline UK samples process- guidance document for representatives
- Certificate of passing the representatives' ABPI examination

PANEL RULING

The Panel noted that GlaxoSmithKline had a policy of posting samples of medicines to health professionals. Representatives were not allowed to hold supplies of samples for distribution. The relevant SOP (dated 24 June 2005) set out the detailed arrangements.

Representatives were allocated one demonstration pack per product which was actual stock overlabelled 'For demonstration purposes only. NOT for clinical use or to be left with customers'. According to the SOP such packs could not be replaced unless there was a very good reason, for example, theft and in such a case a crime reference number was required. Representatives were provided with a guidance document on the arrangements.

The Panel considered that this was a very serious allegation. The complainant provided no evidence regarding the alleged sales of samples. GlaxoSmithKline had provided copies of its SOP, its guidance notes and details of an audit of the representative's samples for the year July 2006 – July 2007. In the last 12 months the representative had requested mainly Incheck devices and placebo inhalers although it appeared that Seretide inhalers might have been ordered for two doctors (the number of samples had not been indicated on the forms) but the requests for Seretide had been rejected. Some of the requests indicated that the sample was to be sent to the practice nurse. The audit form tallied the quantity of samples requested with that ordered, despatched, returned and indicated that the request form had been checked. On the evidence before it the Panel considered that GlaxoSmithKline had an adequate system of control and accountability for samples and medicines. Thus no breach of Clause 17.9 was ruled.

There was no evidence that samples had been provided to a non-health professional as alleged nor without a signed dated written request. No breach of Clauses 17.1 and 17.3 was ruled. The Panel did not consider that either the representative or the company had failed to maintain high standards. Thus no breach of Clauses 15.2 and 9.1 was ruled.

Given its rulings above the Panel did not consider that there had been a breach of Clause 2.

Complaint received	**24 July 2007**
Case completed	**10 September 2007**

CASE AUTH/2029/7/07 and AUTH/2030/7/07

MYOCARDIAL INFARCTION NATIONAL AUDIT PROJECT v SANOFI-AVENTIS AND BRISTOL-MYERS SQUIBB

Sponsored meetings

The Myocardial Infarction National Audit Project (MINAP) complained about the activities of an agency working on behalf of Sanofi-Aventis and Bristol-Myers Squibb and, in particular, an invitation to a meeting.

The complainant noted that MINAP collected and analysed data on acute myocardial infarction from all acute hospitals in England and Wales. It had existed since 2000 and was now one of the world's largest audits of myocardial infarction. It was funded by the Healthcare Commission. Involvement with MINAP was mandatory for acute hospitals and MINAP analyses were used to measure hospital performance and as evidence of collaboration in national audit by the Healthcare Commission.

MINAP had a strong presence within the cardiac community and was widely recognised as a very successful long term national project which had resulted in major improvements in cardiac care. It was highly respected as a source of national data on care for acute myocardial infarction. MINAP had never solicited support from industry; it was the view of the MINAP steering group that MINAP should have no involvement with the pharmaceutical industry.

The complainant stated that in summer 2006 a member of the MINAP steering group told him about a local collaboration in which she and a colleague, together with Bristol-Myers Squibb, would develop a toolkit to assist local hospitals make the best use of MINAP data. The complainant understood that the cost was to be funded by an unrestricted educational grant from Bristol-Myers Squibb.

The complainant stated that on presenting this work to the MINAP steering group his colleague had been advised to proceed with great caution with any involvement with industry, and that MINAP itself would not become directly involved. Nevertheless, on the basis that Bristol-Myers Squibb would support the development of the toolkit the complainant met the agency which was involved in developing the toolkit on behalf of Bristol-Myers Squibb, in order to hear more of its proposals. This consisted of developing the toolkit – on the basis of ideas provided locally – and presenting this work at a series of seminars involving clinicians, nurses, audit staff, and cardiac network staff throughout the country. It was stated by the agency that funding was unrestricted. After the meeting those involved with the project had misgivings about the direction in which it was moving, and in particular it became clear that support was not unrestricted and that they were going to be working on an enterprise which had clear commercial involvement and which would involve promotion, either directly or indirectly, of relevant pharmaceutical products.

As MINAP was a national project funded by the Healthcare Commission it was clearly impossible for it to be involved with such commercial enterprise, and the complainant advised the agency accordingly and considered the matter closed. The complainant's colleagues also withdrew their involvement.

The complainant was surprised therefore to discover that the project had continued and developed into a one day meeting 'Getting the most of MINAP' and with promotional material clearly emphasising a link with the MINAP project. The complainant provided a two page document headed 'Best practice seminars in using MINAP to improve local cardiac care' as an example of the material involved which he alleged had linked the companies sponsoring the meeting with MINAP. The item included the sentence 'The workshop is based on a new toolkit of best practice developed in association with the MINAP Steering Committee and local stakeholders'. As far as the MINAP steering committee was concerned this was false. An association was being made with MINAP – a mainstream and well regarded national project – and the commercial activities of these companies. No association existed and the complainant repudiated any involvement with this project. In Module 3 of the meeting there was to be feedback for the MINAP steering committee. MINAP had never solicited any feedback, nor had it received any. MINAP did not want to be associated with these activities and objected to its name being used in association with meetings sponsored by these pharmaceutical companies.

The complainant was concerned that:

- **MINAP's good name had been used to commercial advantage, without permission and against the wishes of the MINAP steering group;**
- **these activities might be considered a form of disguised promotion;**
- **any suggestion in the promotional literature that MINAP was involved with this project was knowingly false and misleading;**
- **this activity had an adverse impact on MINAP and its relations with the very wide group of individuals who supported it; MINAP had its**

own agenda of information and advice that it wished to impart ie by means of regional visits, and this was being subverted by these meetings.

The Panel noted that the complaint was about a series of meetings sponsored by Sanofi-Aventis and Bristol-Myers Squibb entitled 'Getting the most out of MINAP' although the complainant focussed on the arrangements for one of those meetings. According to the companies the meetings were designed to facilitate improvements in the quality of patient care through the better use of the MINAP audit tool. The meeting content and tool kit was developed by the companies' agency. The Panel did not consider that the companies were prohibited in arranging meetings about MINAP but such meetings had to comply with the Code. It was an established principle that the companies were responsible under the Code for the activities of agencies or other parties acting on their behalf.

The Panel noted the parties' submissions about the development of the toolkit and meeting programme. All agreed that initially the MINAP steering committee and the agency had talked about the meeting programme but that MINAP had subsequently stated that it did not want to have any further involvement with it. Regional MINAP staff also withdrew from the project. The companies submitted that they then took corrective measures to ensure that their material did not reflect an association with MINAP. However due to an error an old invitation was sent by the companies' agency to the meetings administrator who in turn sent it to invitees.

The invitation provided by the complainant was entitled 'Best practice seminars in using MINAP to improve local cardiac care. Getting the most out of MINAP'. A highlighted box, above the agenda, explained that the toolkit of best practice was developed in association with the MINAP steering committee and local MINAP stakeholders. 'Module 3: MINAP in practice' listed as its final bullet point 'Feedback for MINAP steering group'. The Panel considered that the invitation gave a misleading impression of the positive involvement of the MINAP steering committee and suggested that the toolkit was endorsed or otherwise approved by it. The Panel noted that whilst, at the request of MINAP, delegates were told at the outset of each meeting that the programme was not associated with the MINAP steering committee this was not sufficient to correct the otherwise misleading impression given by the invitation. The misleading impression was compounded by the wording of the declaration of sponsorship which explained that 'The toolkit development and workshop is sponsored by Bristol-Myers Squibb Pharmaceuticals Ltd and Sanofi-Aventis'. This implied that the companies' role was limited to financial support which was not so. The meetings and toolkit were in effect developed by the companies, via their agency in consultation with others. High standards had not been maintained. A breach of the Code was ruled. The Panel did not consider that the invitation brought discredit upon and reduced confidence in the pharmaceutical industry.

The Panel noted that in subsequent invitations the reference to the role of MINAP and feedback had been removed. The Panel noted the agenda consisted of three modules: MINAP in the NHS, achieving the benefits and MINAP in practice. Copies of the presentations were provided and these discussed MINAP data under the module headings. There was no product specific material nor were there any exhibition stands at the meetings. The Panel considered that there was no evidence before it to indicate that the meetings were promotional and disguised in this regard. High standards had been maintained and no breach of the Code was ruled.

The Myocardial Infarction National Audit Project (MINAP) complained about the activities of an agency working on behalf of Sanofi-Aventis and Bristol-Myers Squibb, in particular, an invitation to a meeting (ref PLA06/1806).

COMPLAINT

The complainant noted that MINAP collected and analysed data on acute myocardial infarction from all acute hospitals in England and Wales. It had existed since 2000 and was now one of the world's largest audits of myocardial infarction. It was funded by the Healthcare Commission. Involvement with MINAP was mandatory for acute hospitals and MINAP analyses were used to measure hospital performance and as evidence of collaboration in national audit by the Healthcare Commission.

MINAP had a strong presence within the cardiac community and was widely recognised as a very successful long term national project which had resulted in major improvements in cardiac care. It was the end product of many years' hard work, and was highly respected as a source of national data on care for acute myocardial infarction. MINAP had never solicited support from industry; it was the view of the MINAP steering group that MINAP should have no involvement with the pharmaceutical industry.

The complainant stated that in summer 2006 a member of the MINAP steering group told him about a local collaboration in which she and a colleague were involved with Bristol-Myers Squibb which, in essence, involved development of a toolkit to assist hospitals make the best use of MINAP data. At the time this was a local development that the complainant's colleagues saw might be useful. The complainant understood that the cost was to be funded by an unrestricted educational grant from Bristol-Myers Squibb.

The complainant stated that as the general concept was of interest he had invited his colleague to present the work to the MINAP steering group, and this presentation received the (minuted) advice that she should proceed with great caution with any involvement with industry, and that MINAP itself would not become directly involved. Nevertheless, on the basis that Bristol-Myers Squibb would support the

development of the toolkit for the complainant's colleagues, he met the agency which was involved in developing the toolkit on behalf of Bristol-Myers Squibb, in order to hear more of its proposals. This consisted of developing the toolkit – on the basis of ideas provided locally by the complainant's colleagues – and presenting this work at a series of seminars involving clinicians, nurses, audit staff, and cardiac network staff throughout the country. It was stated by the agency that funding was unrestricted. After the meeting the complainant's colleagues had misgivings about the direction that the project was moving, and in particular it became clear that support was not unrestricted and that they were going to be working on an enterprise which had clear commercial involvement and which would involve promotion, either directly or indirectly, of relevant pharmaceutical products.

The complainant submitted that as MINAP was a national project funded by the Healthcare Commission it was clearly impossible for it to have any involvement with such commercial enterprise, and he advised the agency accordingly and considered the matter closed. The complainant's colleagues also withdrew their involvement.

The complainant was surprised therefore to discover that the project had continued and developed into a one day meeting 'Getting the most of MINAP' and with promotional material clearly emphasising a link with the MINAP project. The complainant provided a two page document headed 'Best practice seminars in using MINAP to improve local cardiac care' which was an example of the material involved which he alleged had linked the companies sponsoring the meeting with MINAP. The item included the sentence 'The workshop is based on a new toolkit of best practice developed in association with the MINAP steering committee and local stakeholders'. As far as the MINAP Steering Committee was concerned this was false. An association was being made with MINAP – a mainstream and well regarded national project – and the commercial activities of these companies. No association existed and the complainant repudiated any involvement with this project. In Module 3 of the meeting (shown in the item) it was stated that there was to be feedback for the MINAP steering committee. MINAP had never solicited any feedback, nor had it received any. MINAP did not want to be associated with these activities and objected to its name being used in association with meetings sponsored by these pharmaceutical companies.

The complainant was concerned that:

- the good name of MINAP had been used to commercial advantage, without permission and against the wishes of the MINAP steering group;
- these activities might be considered a form of disguised promotion;
- any suggestion in the promotional literature that MINAP was involved with this project was knowingly false and misleading;
- this activity had an adverse impact on MINAP and its relations with the very wide group of individuals who supported it; MINAP had its own agenda of information and advice that it wished to impart ie by means of regional visits, and this was being subverted by these meetings.

When writing to the companies the Authority asked them to respond in relation to Clauses 2 and 9.1 of the Code.

RESPONSE

Sanofi-Aventis and Bristol-Myers Squibb submitted that the 'Getting the most out of MINAP' meetings programme sponsored by them and delivered on their behalf by their agency was a series of educational meetings designed to help health professionals who had to capture and work with MINAP data. The meetings were offered to health professionals within cardiac networks who acted as partners in the subsequent delivery of the local programme. Delegates included staff from ambulance services, acute hospital trusts, cardiac networks and primary care trusts (PCTs).

The companies submitted that the meetings were non-promotional and hence there was no product mentioned in the agenda or content of the meeting, neither were there any promotional stands at the event. The meetings aimed to facilitate improvements in the quality of patient care through the better use of the MINAP audit tool.

The companies submitted that, as stated by the complainant and during the development of the meeting programme, their agency had talked with members of the MINAP steering group and the complainant. During this dialogue the companies were advised that MINAP did not want any further involvement with their programme and so corrective measures were taken to ensure that materials did not reflect an association with MINAP. These changes were undertaken prior to the first local meeting in this programme (flyer provided).

The companies submitted that further, on the advice of MINAP, they undertook to verbally communicate at the outset of each meeting that the programme was not associated with the MINAP steering group. A senior officer of MINAP had also presented at one of the subsequent meetings.

The companies explained the approach taken in the organisation of the particular meeting referred to by the complainant:

- About ten weeks before the meeting took place the companies' local Healthcare Manager approached a cardiac network director and explained the objectives and programme content of the meeting so as to gauge initial interest and where appropriate identify potential areas for local focus.

- Following this initial meeting, the agency contacted the cardiac network director to clarify the programme content and agree on local issues relating to MINAP that needed to be considered.

For the region this included how to improve the quality of data in MINAP, agreement on provisional dates and the venue for the meeting, agreement on any local presenters and the identification of a network administrator who then emailed potential delegates with an approved flyer. In this regard the companies acknowledged that a previously approved version of the flyer was erroneously sent by the agency to the administrator.

- Delivery of actual event: arrangements for the venue, catering and other logistics were co-ordinated either by the companies or the agency, in accordance with the Code. The meeting was non-promotional. There were no promotional stands at the event, neither was there any other form of promotional activity at the event.

The companies provided copies of the materials relating to the meeting.

The companies submitted that the flyer used for the meeting was not the most up-to-date version as it had been superseded by one developed earlier in preparation for the first local meeting of this programme. The changes in the amended material had addressed the complainant's concerns as reference to MINAP's involvement in the development of this programme and feedback being given to the MINAP steering group had been removed.

The companies submitted that it was unfortunate that the obsolete version of the flyer was used instead of the updated document. In order to avoid this happening again, the companies had asked its agency to destroy any previous versions of materials that it might have which had been prepared for these meetings. The agency confirmed on 9 August that this had been done.

Specific concerns of complainant

1 'That the good name of MINAP had been used to commercial advantage, without permission and against the wishes of the MINAP Steering Group'

The companies reassured the Authority and MINAP that the main objective of the meetings programme was to ensure optimal local use of the MINAP audit tool, to ultimately lead to enhancements in patient care. This type of educational meeting was analogous to provision of education to local stakeholders on optimal implementation of other types of national, government-led initiatives such as National Institute for Health and Clinical Excellence (NICE) guidelines or the General Medical Services (GMS) contract

The companies reiterated that updated materials addressed the issues raised by the complainant and did not refer to any involvement of the MINAP group in the development of the programme or to feedback being given to the MINAP steering group.

Further, on the advice of MINAP, the companies, at the beginning of each meeting, verbally communicated that the programme material was not directly associated with the MINAP steering group and that no association could be made subsequently. This disclaimer was communicated at the beginning of the meeting in question; the companies had written confirmation that this had happened at the meeting in question.

2 'That these activities might be considered a form of disguised promotion'

The companies reiterated that the meeting was non-promotional with no mention of product and no promotion either at the meeting or during any activities surrounding its preparation. Also, the companies reassured the Authority and MINAP steering group that this programme had been set up as a support to local cardiac networks in order to improve their understanding and use of MINAP. The main aim of these meetings was to work in partnership with local networks to enhance patient care through optimising the use of an existing national audit tool.

3 'That any suggestion in the promotional literature that MINAP had any involvement with this project was knowingly false and misleading'

The companies reiterated that all materials were non-promotional and any mention of involvement of the MINAP steering group in the development of this programme had been removed after communication with it. The flyer provided by the complainant was used in error on this occasion. As mentioned above, the companies had also undertaken to clearly communicate at each meeting that the MINAP group was not involved in the development of these meetings during the introduction at each meeting.

4 'That this activity had an adverse impact on MINAP and its relations with the very wide group of individuals who supported it'

The companies submitted that they stood behind the quality and non-promotional nature of this programme and sincerely regretted any error or misunderstanding that might have occurred.

The companies submitted that the meetings were intended as a facilitated discussion forum for MINAP users and/or health professionals familiar with the system in order to increase their knowledge on the use and potential implications of MINAP at local level, with the end objective of enhancing patient care through optimising use of this audit tool. They were also a good opportunity for sharing best practice on the use of MINAP (ie how to improve data collection and quality). It was important to clarify that MINAP software was not used during the meetings and all the materials used were developed by the agency on behalf of the companies.

In summary, the companies wished to reassure both the Authority and MINAP that this meeting was non-promotional and carried out in good faith to enhance understanding of MINAP in order to ultimately enhance patient care.

PANEL RULING

The Panel noted that the complaint was about a series of meetings sponsored by Sanofi-Aventis and Bristol-Myers Squibb entitled 'Getting the most out of MINAP' although the complainant focussed on the arrangements for one of those meetings. According to the companies the meetings were designed to facilitate improvements in the quality of patient care through the better use of the MINAP audit tool. The meeting content and tool kit was developed by the companies' agency. The Panel did not consider that the companies were prohibited from arranging meetings about MINAP but such meetings had to comply with the Code. The Panel noted that it was an established principle that the companies were responsible under the Code for the activities of agencies or other parties acting on their behalf.

The Panel was concerned that the invitation to the meeting in question provided by the complainant differed from that provided by the companies although each bore the same reference number. The highlighted box and relevant part of the agenda however were identical. The Panel made its ruling on the basis of the invitation provided by the complainant.

The Panel noted the parties' submissions about the development of the toolkit and meeting programme. All agreed that initially the MINAP steering committee and the agency had talked about the meeting programme but that MINAP had subsequently stated that it did not want to have any further involvement with it. Regional MINAP staff also withdrew from the project. The companies submitted that they then took corrective measures to ensure that their material did not reflect an association with MINAP. However due to an error an old invitation was sent by the companies' agency to the meetings administrator who in turn sent it to invitees.

The invitation provided by the complainant was entitled 'Best practice seminars in using MINAP to improve local cardiac care. Getting the most out of MINAP'. A highlighted box, above the agenda, explained that the toolkit of best practice was developed in association with the MINAP steering committee and local MINAP stakeholders. 'Module 3: MINAP in practice' listed as its final bullet point 'Feedback for MINAP steering group'. The Panel considered that the invitation gave a misleading impression of the positive involvement of the MINAP steering committee and suggested that the toolkit was endorsed or otherwise approved by it. The Panel noted that whilst, at the request of MINAP's deputy clinical director, delegates were told at the outset of each meeting that the programme was not associated with the MINAP steering committee, this was not sufficient to correct the otherwise misleading impression given by the invitation. The misleading impression was compounded by the wording of the declaration of sponsorship which explained that 'The toolkit development and workshop is sponsored by Bristol-Myers Squibb Pharmaceuticals Ltd and Sanofi-Aventis'. This implied that the companies' role was limited to financial support which was not so. The meetings and toolkit were in effect developed by the companies, via their agency in consultation with others. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel did not consider that the invitation brought discredit upon and reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

The Panel noted that in subsequent invitations the reference to the role of MINAP and feedback had been removed. The Panel noted the agenda consisted of three modules: MINAP in the NHS, achieving the benefits and MINAP in practice. Copies of the presentations were provided and these discussed MINAP data under the module headings. There was no product specific material nor were there any exhibition stands at the meetings. The Panel considered that there was no evidence before it to indicate that the meetings were promotional and disguised in this regard. High standards had been maintained. No breach of Clause 9.1 was ruled. Accordingly, the Panel ruled no breach of Clause 2 on this point.

Complaint received	**2 August 2007**
Cases completed	**25 September 2007**

FORMULARY MANAGER v ASTRAZENECA

Conduct of representative

A formulary manager at a hospital NHS Trust, complained about the conduct of a representative from AstraZeneca in relation to the promotion of Crestor (rosuvastatin).

Crestor had been turned down by the drug and therapeutics committee (D&TC) in February 2007. The representative had not come to the pharmacy to find out the decision but proceeded to discuss the benefits of the product with several key consultants.

In August when the representative contacted the complainant to find out the decision, the representative queried it and continued to argue the merits of the product. The sensitivity required and respect for the local decision of the trust was neither appreciated nor adhered to. For these reasons the representative was asked not to visit the trust and to contact the chief pharmacist of the primary care trust (PCT) if the representative wished to discuss Crestor with local GPs.

The Panel noted from AstraZeneca that the representative had tried to make an appointment with pharmacy to discuss the outcome of the D&TC decision but was turned away at the reception desk. The Panel noted that the PCT did not have a formal policy for seeing representatives. The representative appeared to have been told by the chief cardiologist in February that Crestor was on the formulary and in May that that was no longer so. The representative continued to promote Crestor to consultants conveying the formulary status. In August the representative and the complainant had met to discuss why the Crestor application had been rejected.

The Panel noted that the complainant had not commented upon or provided a copy of the email stating that Crestor was on the formulary which AstraZeneca submitted had been sent by the complainant to the chief cardiologist

The Panel noted that there was no formal policy regarding the conduct of representatives at the trust. It was not necessarily a breach of the Code to promote a product that was not on the formulary.

The Panel noted that the parties' accounts were different but not inconsistent. It was not unreasonable for a representative to query a decision and discuss the merits of that decision. Whilst so doing, the Code required representatives to maintain a high standard of ethical conduct. The Panel was concerned about AstraZeneca's submission that the representative accepted that she was, *inter alia*, facetious during her conversation with the complainant. However this was not specifically mentioned by the complainant.

The Panel considered that with regard to the representative discussing the D&TC decision there was some confusion. There was insufficient evidence to show that on the balance of probabilities the representative had not visited the pharmacy to find out the decision as alleged by the complainant.

The Panel considered that given all the circumstances there was no breach of the Code and thus ruled accordingly.

A formulary manager at a hospital NHS Trust complained about the conduct of a representative from AstraZeneca in relation to the promotion of Crestor (rosuvastatin).

COMPLAINT

The complainant stated that Crestor had been turned down by her drug and therapeutics committee (D&TC) in February 2007. The representative had not come to the pharmacy to find out the decision but proceeded to discuss the benefits of the product with several key consultants. The representative circulated views between consultants and continued to promote the product's perceived benefits.

When finally in August the representative contacted the complainant to find out the decision, the representative queried it and continued to argue the merits of the product. The sensitivity required and respect for the local decision of the trust was neither appreciated nor adhered to. For these reasons the representative was asked not to visit the trust and to contact the chief pharmacist of the local primary care trust (PCT) if the representative wished to discuss Crestor with local GPs.

When writing to AstraZeneca to inform it of the complaint, the Authority asked it to respond to the requirements of Clauses 15.2 and 15.4 of the Code.

RESPONSE

AstraZeneca submitted that it took all allegations of inappropriate conduct very seriously and as soon as the complainant contacted it directly in August, it started an immediate investigation. Pending the outcome of this, the representative was informed by her line manager on the next day that she would not work in local PCTs or its hospitals until further notice. AstraZeneca telephoned the complainant twice in August and had a lengthy discussion about what had transpired, her concerns, corrective actions and future communications.

The representative in question had been with the company since 2001 and had passed her ABPI examination.

The representative's last training course was in 2007 and she was validated by internal and external assessors (a PCT prescribing lead). The details were provided. Her performance ratings for the past 2 years had been excellent. In addition, in July 2007 she signed off 14 corporate governance policies including the ABPI Code – for 10 of the policies (including the Code) achieving a 100% pass rate on her first attempt. A previous manager described the representative as 'an excellent rep' with 'good rapport' with her customers. Her key strengths being her ability to challenge and her clinical data knowledge – both of which lent themselves to confidence in front of customers. One of the representative's customers, (a cardiologist) stated that 'her professional conduct is exemplary'.

The D&TC met in February 2007 and considered the inclusion of Crestor onto the formulary. A thorough literature review was conducted, lots of debate ensued and the decision to reject the application was not made lightly. Although the complainant stated that all representatives were briefed by pharmacy to contact it with regards to D&TC decisions, the representative had tried on many occasions to see the complainant to determine what decision had been reached and how, but she was turned away at the pharmacy reception desk. It was evident that pharmacy had not communicated any policy to her on when the complainant saw representatives. This concurred with the complainant's statement that the representative never saw her after the D&TC's decision was made and no hospital policy was available for any representative to see (and therefore adhere to).

The representative stated that a chief cardiologist told her in February that Crestor was on the formulary and she wanted to see pharmacy to see when and how it would issue guidance to the hospital but was unable to see the complainant. Although the chief cardiologist was unavailable for interview as he was currently on annual leave, his colleague, a cardiologist, corroborated this statement because on more than one occasion he was a witness when the chief cardiologist verbally told the representative that Crestor was on the formulary.

According to the representative, a few months before May the complainant had emailed the chief cardiologist, stating Crestor was on the formulary and she saw this email. AstraZeneca was unable to trace this email as the chief cardiologist was at present on annual leave. The representative believed that the decision was then overturned by the complainant. The cardiologist recalled that there was some confusion with clinicians as to the formulary status of Crestor and noted that at one new medicines committee meeting, the chief cardiologist said he thought Crestor was on the formulary and was surprised that it wasn't. The cardiologist stated 'poor [the representative] is an innocent victim of miscommunication'.

AstraZeneca submitted that in May the chief cardiologist told the representative that Crestor was not on the formulary. She continued to promote the product to consultants, conveying to them the formulary status, talked to them about where they used it, discussed referrals, the opinion of the PCT and what needed to be done to get it accepted onto the formulary next time. Although the complainant considered that the representative should not have promoted Crestor at all, in the absence of any such hospital policy directing this, the representative continued to do her job.

AstraZeneca submitted that in August, the representative met the complainant to discuss why the Crestor application had been rejected. When the representative mentioned the email from the complainant to the chief cardiologist, she immediately recognised that the complainant thought she was rude and not understanding but she alleged that she was 'privy to information she (the complainant) didn't want me to have, no one likes to be proved wrong'. The representative accepted that she was challenging and facetious during their conversation.

In conclusion from internal investigations it was apparent that the representative respected and understood the D&TC and its decisions and did not promote Crestor as being on formulary as soon as she knew of this change and accepted that she was facetious in August during a conversation with the complainant. Further discussions with the representative would establish next steps, in terms of her behaviour going forwards and her role within the NHS trust.

AstraZeneca submitted that the corporate compliance leader had apologised unreservedly to the complainant on behalf of the representative, for any inappropriate behaviour or conduct, or if any offence was taken. In addition, she had reassured the complainant that AstraZeneca would write to the chief pharmacist and the complainant and agree to abide by the local arrangements in place with respect to the representative and the promotion of Crestor.

AstraZeneca submitted that with respect to the allegation of misconduct, it was extremely disappointed that a member of the hospital trust felt compelled to complain to the PMCPA. The company was confident that the representative had maintained a high standard of ethical conduct in the discharge of her duties and, on this occasion, as the conversation was between two parties with no witnesses, it was difficult for anyone else to judge what occurred and draw an absolute conclusion. Nevertheless AstraZeneca apologised unreservedly if any offence was taken but did not accept that it was in breach of Clause 15.2.

With respect to Clause 15.4, all parties accepted that there were no local arrangements in place and therefore AstraZeneca submitted that it was not in breach of this clause.

Further comments from the complainant
The complainant was asked to comment on AstraZeneca's response before the Panel made its ruling.

The complainant stated that to her knowledge, no attempt was made to make an appointment with pharmacy to ascertain the trust decision regarding Crestor. Time was allocated to ensure that communications were clear and unambiguous and to facilitate adherence to trust decisions by representatives. There were no records that appointments were made by the representative.

Although the trust did not have a formal policy for representatives at present, good practice of representatives and the availability of pharmacy to meet with representatives to confirm formulary status avoided unacceptable promotion of non formulary medicines.

The complainant noted the statement 'On [May] the representative was informed … that Crestor was not on the formulary. She continued to promote the product to consultants …'. This contradicted the statement in the conclusion '[the representative] …stopped promoting Crestor as being on formulary as soon as she was made aware of this change …'.

PANEL RULING

The Panel noted from AstraZeneca that the representative had tried to make an appointment with pharmacy to discuss the outcome of the D&TC decision but was turned away at the reception desk. The Panel noted that the trust did not have a formal policy for seeing representatives. The representative appeared to have been told by the chief cardiologist in February that Crestor was on the formulary and in May that that was no longer so. The representative continued to promote Crestor to consultants conveying the formulary status. In August the representative and the complainant had met to discuss why the Crestor application had been rejected.

The Panel noted that the complainant had not commented upon or provided a copy of the email stating that Crestor was on the formulary. AstraZeneca submitted that this had been sent by the complainant to the chief cardiologist.

The Panel noted that there was no formal policy regarding the conduct of representatives at the trust. It was not necessarily a breach of the Code to promote a product that was not on the formulary.

The Panel considered that AstraZeneca's response was not contradictory as suggested by the complainant. The representative had not stopped promoting Crestor but had stopped promoting it as being on the formulary.

The Panel noted that the parties' accounts were different but not inconsistent. It was not unreasonable for a representative to query a decision and discuss the merits of that decision. Whilst so doing, the Code required representatives to maintain a high standard of ethical conduct. The Panel was concerned about AstraZeneca's submission that the representative accepted that she was, *inter alia*, facetious during her conversation with the complainant. However this was not specifically mentioned by the complainant.

The Panel considered that with regard to the representative discussing the D&TC decision there was some confusion. There was insufficient evidence to show that on the balance of probabilities the representative had not visited the pharmacy to find out the decision as alleged by the complainant.

The Panel considered that given all the circumstances there was no breach Clauses 15.2 and 15.4 of the Code.

Complaint received	**2 August 2007**
Case completed	**24 October 2007**

CASE AUTH/2034/8/07

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY v RECORDATI

Tradorec XI Leavepiece

The Medicines and Healthcare products Regulatory Agency (MHRA) complained about a Tradorec XL (tramadol) leavepiece issued by Recordati. Page three of the leavepiece featured a box headed 'MHRA advice:' followed by 'Prolonged Release preparations should be prescribed by brand, with no generic substitution'. The claim was referenced to 'Personal Communication. Recordati Pharmaceuticals Ltd'.

The MHRA stated that it had recently received a complaint which alleged there was no justification for the inclusion of the 'MHRA advice' on prescribing by brand in the leavepiece and that this was misleading. The MHRA alleged that reference to 'MHRA advice' was a clear breach of the Code and therefore referred this aspect to the Authority.

The Panel was extremely concerned to note that emails to the MHRA from Recordati had been sent by a consultant to the company who described himself in the emails as an independent pharmaceutical consultant without noting at the same time that he was writing on behalf of Recordati or any other pharmaceutical company. One email referred to tramadol. Neither of the emails sent to the MHRA referred to the proposed use of the information in promotional literature. The Panel considered that Recordati had not been transparent in its correspondence with the MHRA.

The Panel noted that the MHRA, without being told the intention behind the correspondence, had in effect given permission to the pharmaceutical consultant to show the email correspondence to health professionals. The MHRA had not specifically required Recordati to include such a reference in its promotional material, thus even if Recordati had fully informed permission from the MHRA it would nonetheless be unacceptable to mention the MHRA in promotional material. The Panel therefore ruled a breach of the Code.

The Medicines and Healthcare products Regulatory Agency (MHRA) complained about a Tradorec XL (tramadol) leavepiece (ref TRA06-0020) issued by Recordati Pharmaceuticals Ltd.

Page three of the leavepiece featured a box headed 'MHRA advice:' followed by 'Prolonged Release preparations should be prescribed by brand, with no generic substitution'. The claim was referenced to 'Personal Communication. Recordati Pharmaceuticals Ltd'.

COMPLAINT

The MHRA had recently received a complaint which alleged there was no justification for the inclusion of the 'MHRA advice' on prescribing by brand in the leavepiece and that this was misleading. The MHRA was minded to take the view that the leavepiece was misleading and in potential breach of Regulation 3A(3) of the Medicines (Advertising) Regulations 1994. It was currently investigating this case.

The MHRA alleged that reference to 'MHRA advice' was a clear breach of Clause 9.5 of the Code and therefore referred this aspect to the Authority.

RESPONSE

Recordati denied a breach of Clause 9.5 because it had explicit permission from the MHRA Information Centre to share its advice on the prescribing of modified/prolonged release preparations with NHS workers, including GPs; the leavepiece reflected that permission.

Recordati explained that before it launched Tradorec XL a consultant to the company emailed the MHRA Information Centre to ask if it had any advice on the prescribing of once daily formulations of tramadol. Two responses were received which although worded slightly differently were both clear that brand or invented names should be used when writing or prescribing modified/prolonged release preparations. The consultant emailed the MHRA Information Centre again to ask whether its reply could be shown to workers in the NHS. The reply confirmed that it could be.

Having been told that modified/prolonged release preparations should be prescribed by brand/invented name and having asked for and received permission from the MHRA to show this advice to workers in the NHS, Recordati believed it had complied with both the spirit and letter of Clause 9.5.

PANEL RULING

The Panel noted that Clause 9.5 prohibited reference in promotional material to *inter alia* the MHRA. The only exemption to this prohibition was if such reference was specifically required by the licensing authority.

The Panel was extremely concerned to note that the emails to the MHRA from Recordati had been sent by a consultant to the company who described himself in the emails as an independent pharmaceutical consultant without noting at the same time that he was

writing on behalf of Recordati or any other pharmaceutical company. One email referred to tramadol. Neither of the emails sent to the MHRA referred to the proposed use of the information in promotional literature. The Panel considered that Recordati had not been transparent in its correspondence with the MHRA.

The Panel noted that the MHRA, without being told the intention behind the correspondence, had in effect given permission to the pharmaceutical consultant to show the email correspondence to health professionals. The MHRA had not specifically required Recordati to include such a reference in its promotional material, thus even if Recordati had fully informed permission from the MHRA, given the wording of Clause 9.5 it would nonetheless be unacceptable to mention the MHRA in promotional material. The Panel therefore ruled a breach of Clause 9.5.

Complaint received	**10 August 2007**
Case completed	**6 September 2007**

CASE AUTH/2035/8/07

CONSULTANT DERMATOLOGIST v LEO PHARMA

Dovobet 'Dear Doctor' letter

A consultant dermatologist alleged that a letter from Leo Pharma recommended that most psoriasis patients on Dovonex Ointment (calcipotriol; discontinued) would be appropriately switched to Dovobet Ointment (calcipotriol/betamethasone). This was not the case. These were two distinct treatments, one a potent to very potent topical corticosteroid and the other a non-corticosteroid vitamin D analogue. The complainant alleged that to recommend a direct switch was inappropriate and put patient safety at risk.

By way of background, the complainant made general comments about the relative efficacy and safety of corticosteroid or corticosteroid/vitamin D analogues in psoriasis. In particular the complainant noted that it was important that both prescribers and patients knew that Dovobet contained a potent corticosteroid and were thus alert to possible side effects associated with such therapy. The complainant was suspicious that the 'diminished clinical usefulness' of Dovonex Ointment coincided with the UK patent expiry.

The complainant stated that the main issues were:

- **The letter suggested switching from Dovonex to Dovobet Ointment which, especially if carried out by those without particular experience in managing psoriasis could endanger patient safety.**
- **The UK withdrawal of Dovonex Ointment (but not cream, which was not produced generically), without much notice and without waiting for a generics manufacturer to take over production of an equivalent preparation (and assisting patients in being transferred over to this from Dovonex Ointment), while Leo was promoting Dovobet Ointment might make commercial sense. However, these actions were disappointing; perhaps naively the complainant should have liked to believe the letter's introductory paragraph claiming that the sole purpose of the Leo foundation was to research, develop and market efficacious treatments for the benefit of patients. This approach to promotion brought discredit upon, and reduced confidence in, the pharmaceutical industry.**

The Panel noted the complainant's explanation that he had commented on a number of general points by way of background. He did not however make specific allegations about these points. The Panel considered that it had specific allegations about whether the letter implied that patients should be switched from Dovonex Ointment to Dovobet and associated safety issues and the withdrawal of Dovonex.

The letter stated 'because the clinical usefulness of Dovonex Ointment (calcipotriol 50 micrograms/g) has diminished it is no longer supplied by Leo Pharma in the UK. As a result and in response to enquiries we are continuing to receive we would advise that for the majority of your patients, Dovobet (calcipotriol 50 micrograms/g, betamethasone 0.5 milligrams/g) can replace Dovonex Ointment (calcipotriol 50 micrograms/g)'. There followed discussion of Dovobet's efficacy.

There were important differences between the products. Dovobet was indicated for the topical treatment of stable plaque psoriasis whereas Dovonex Ointment was indicated more broadly for the topical treatment of plaque psoriasis. Dovobet had a recommended treatment period of four weeks after which repeated treatment could be initiated under medical supervision; there was no recommended treatment period for Dovonex. Dovobet was not recommended for use in children and adolescents below the age of 18 years whereas Dovonex Ointment could be used with care, and with some restrictions as to maximum weekly dose, in children aged 6 and above. There was limited experience of the use of Dovonex in children under 6 years and a maximum safe dose in that group had not been established. The Dovonex Ointment summary of product characteristics stated that in respect of children clinical experience had shown Dovonex to be safe and effective over eight weeks at a mean dose of 15g per week but with wide variability in dose amongst patients. In addition Dovobet contained a strong, potent topical corticosteroid and had a more extensive list of contraindications and special warnings and precautions for use than Dovonex.

The letter had a broad circulation including hospital and retail pharmacists, practice nurses, prescribing nurses as well as GPs and consultant dermatologists. The Panel considered that by stating that Dovobet could replace Dovonex Ointment for *the majority* of patients (emphasis added) without making the important differences between the products clear, the letter implied that most patients could be simply switched and that was not necessarily so. There were substantial differences between the products and any switch would have to be conducted with care and on a case by case basis. Dovobet was not recommended for use in patients below the age of 18 years. The reference later in the letter to Dovonex Cream as an option for patients ineligible for treatment with Dovobet did not negate the impression from the preceding paragraphs. The letter was misleading and could not be substantiated in that regard. Breaches of the Code were ruled.

The Panel noted the complainant's allegation that

switching from Dovonex to Dovobet, if carried out by those without particular experience in managing psoriasis could endanger patient safety and that it was important that prescribers were fully aware that they were using a potent steroid and to be alert to its side effects. The letter referred to 'Dovobet's established and reassuring safety profile'. The Panel noted its ruling above about the impression given by the letter and considered that within the context of a letter which advocated a switch from a non-steroidal treatment to a medicine containing a potent steroid it was important that the material fairly represented Dovobet's risk benefit profile. This was especially important given the wide circulation of the letter in question. The Panel considered that the failure to alert readers to the differing side effect profile of Dovobet versus Dovonex was misleading as alleged; the reference to the prescribing information would not suffice in this regard. A breach of the Code was ruled.

The Panel considered that the failure to make it clear that there were important differences between the products, noting in particular the differences in their side effect profiles, meant that the company had failed to maintain high standards. A breach of the Code was ruled. On balance the Panel did not consider that in this regard the material brought discredit upon or reduced confidence in the pharmaceutical industry.

The Panel noted the complainant's concern about the withdrawal of Dovonex Ointment from UK supply. The Panel noted that whilst discontinuation of products might give rise to concern and disappointment it was nonetheless a legitimate business activity. The Panel considered that the principle of product discontinuation was *prima facie* outside the scope of the Code. However any reference to product discontinuation within a promotional letter must comply with the Code. The Panel did not consider that the reference to Dovobet's discontinuation within the context of the letter failed to maintain high standards or brought discredit upon or reduced confidence in the pharmaceutical industry as alleged.

A consultant dermatologist complained about a letter (ref 1008/10488) dated 26 June from Leo Pharma which promoted Dovobet (calcipotriol/betamethasone) and also referred to the discontinuation of Dovonex Ointment (calcipotriol).

COMPLAINT

The complainant noted that the letter advised recipients that since Leo stopped supplying Dovonex Ointment in the UK (in April 2007), '…for the majority of your patients, Dovobet (calcipotriol 50 micrograms/g, betamethasone 0.5 milligrams/g) can replace Dovonex Ointment (calcipotriol 50 micrograms/g)'. The complainant alleged that this read as a direct recommendation that most psoriasis patients on Dovonex Ointment would be appropriately switched to Dovobet Ointment. This was not the case. These were two distinct treatments, one a potent to very potent topical corticosteroid and the other a non-corticosteroid vitamin D analogue. The complainant alleged that to recommend a direct switch was inappropriate and put patient safety at risk.

The complainant agreed that Dovobet was, as stated in the letter, more effective than its corticosteroid component betamethasone dipropionate (Diprosone) alone (Douglas *et al* 2002 and Kaufmann *et al* 2002). The complainant had not seen any studies to determine whether this slight to modest (but unlikely to be chance, that was statistically significant) greater efficacy was due to a synergy of the two compounds in Dovobet. Or was Dovobet, because of the vehicle required to allow mixing of the two main components, a more potent topical corticosteroid than betamethasone dipropionate ointment alone? The complainant considered that betamethasone dipropionate was probably, at least in clinical efficacy, a more potent steroid than the more commonly used betamethasone valerate, although both were in the same broad 'potent' class. Potent topical steroids, when used cautiously, had a place in psoriasis treatment. The letter stated that Dovobet had proved more cost effective than use of the two main constituents concomitantly. The complainant would like to know if any of these studies involved a direct comparison of clinical efficacy and cost effectiveness of once-daily Dovobet Ointment versus alternate days once-daily Diprosone and Dovonex.

However, regardless of the efficacy of Dovobet, it was a potent topical corticosteroid. As well as all the usual topical corticosteroid side effects there had to be particular concern about psoriasis rebound and exacerbation (including the risk of potentially fatal generalised pustular psoriasis, as listed in the prescribing information). Although follow-up under the carefully controlled conditions of a study had been fairly reassuring as regards early (within 1 year) adverse effects (Kragballe *et al* 2006) it was important that prescribers and more importantly, patients, were fully aware that they were using a potent steroid and to be alert to its side effects. Although it was fairly reassuring that a one-year study comparing three regimens (4 weeks of Dovobet then Dovonex Ointment, 1 year of alternating 4 week periods of Donovex Ointment alone and of Dovobet Ointment, 1 year of Dovobet Ointment) did not reveal more side effects generally (including the sometimes troublesome but rarely serious irritant side effects of Dovonex Ointment), 10 of 212 patients on the continuous Dovobet Ointment compared with 6 of 213 and 6 of 209 in the other groups had, 'adjudicated corticosteroid reactions'. Also, the report did not state what happened after one year of Dovobet Ointment – how many study participants had to be admitted or receive outpatient hospital therapy because of rebound psoriasis flares after completion of the study? (Thind and White 2006). This lack of reports of serious side effects probably reflected the expectation that Dovobet, a potent corticosteroid, would cause potent topical corticosteroid side effects, including rebound worsening of psoriasis, so that few thought to report side effects even when severe enough to require

referral to hospital (the complainant had seen several such cases, but never reported them).

The complainant stated that when he received the letter at issue he was already concerned about the marketing of Dovobet. First, Dovonex Ointment was withdrawn in April 2007 suspiciously coinciding with the expiry of the UK patent. In response to patient and GP queries the complainant noted that a generics company now manufactured calcipotriol ointment. On receipt of the letter at issue the complainant noted the statement about Dovonex Ointment no longer being supplied by Leo in the UK because of diminished clinical usefulness and so tried to find out if its usefulness had diminished equally in other countries. It was still listed as a product on Leo's South American website but the North American psoriasis patient association website commented that it was becoming difficult to obtain – the complainant hoped he was being over-suspicious when he wondered if the expiry of US patent protection coming on 12/08/2007 was related.

The main issues were:

- The letter suggested switching from Dovonex to Dovobet Ointment which, especially if carried out by those without particular experience in managing psoriasis (the complainant did not know if Leo's letter was only sent to consultant dermatologists or also to GPs) could, if done without extreme care and case by case selection of appropriate patients, be dangerous to patient safety.
- The UK withdrawal of Dovonex Ointment (but not cream, which was not produced generically), without much notice and without waiting for a generics manufacturer to take over production of an equivalent preparation (and assisting patients in being transferred over to this from Dovonex Ointment), while Leo was promoting Dovobet Ointment might make commercial sense. However, these actions were disappointing; perhaps naively the complainant should have liked to believe the introductory paragraph to the letter claiming that the sole purpose of the Leo foundation was to research, develop and market efficacious treatments for the benefit of patients. This approach to promotion brought discredit upon, and reduced confidence in, the pharmaceutical industry.

When writing to Leo the Authority asked it to bear in mind the requirements of Clauses 2, 7.2, 7.4, 7.9 and 9.1 of the code.

RESPONSE

Leo submitted that the letter was sent to all consultant dermatologists, GPs, dermatology nurses, district nurses, prescribing nurses, practice nurses, hospital pharmacists and retail pharmacists. This letter was sent subsequent to Leo's discontinuation of Dovonex Ointment in the UK market in April 2007 and in response to continuing enquiries from health professionals regarding suitable alternative treatments.

The letter was primarily intended to be informative, as a general response to the enquiries received by Leo. The company had accepted, however, that it also promoted Dovobet and Dovonex Cream and in that regard the requirements of the Code were followed.

Leo disagreed with the complainant's view that it was inappropriate for it to recommend a direct switch from Dovonex Ointment to Dovobet Ointment as they were two distinct treatments and such recommendation put patient safety at risk. The complainant had over-emphasised the degree of interchangeability between the products which the letter conveyed. The complainant admitted that when he received the letter he was already concerned about the marketing of Dovobet and Leo feared this might have coloured his response and led him to misinterpret the letter's meaning.

Leo agreed that Dovobet was not a straightforward replacement for Dovonex because Dovobet had an additional active ingredient which changed the safety profile and posology. However, a treatment regimen based upon Dovobet could satisfactorily replace a treatment regimen based on Dovonex in most patients.

It was this message that Leo's letter was intended to convey in a concise fashion. Not that the products were directly interchangeable as one element within an unchanged regimen but that treatment with one could replace treatment with the other. Both products had the same indication and for the most part were prescribed for similar types of patients, at the same stage of disease and in similar treatment regimens. The letter qualified the statement thus: 'for the majority of your patients, Dovobet … can replace Dovonex Ointment…'.

Leo had not recommended an automatic or direct switch and had not recommended that Dovobet should be used in all patients previously treated with Dovonex but only in those for whom it was suitable and with appropriate adjustment of the supporting elements of the treatment regimen. Leo used the phrase 'Dovobet can replace' as opposed to 'Dovobet is replacing', ie the replacement was optional not mandatory.

Leo stated that in its letter it justified why it believed Dovobet a suitable alternative and described how Dovobet should be used correctly with appropriate advice on maximum dosage and medical supervision of repeated courses. This advice was specific to Dovobet and did not imply that there should be a direct switch between products. On the contrary, giving such specific information on appropriate use implied that there were differences between the products that should be considered when prescribing. The letter included the advice that for patients ineligible for treatment with Dovobet, Dovonex Cream might be a suitable alternative. This explicitly acknowledged that there were differences between the products and that not all Dovonex-treated patients were suitable for Dovobet. The eligibility of the patient for Dovobet treatment needed to be considered. The prescribing information also made the differing side effect profiles and dosage and administration advice between the products apparent.

To summarise, Leo accepted and agreed with the complainant's concern that Dovonex should not be switched to Dovobet without care and case by case selection, however it did not intend, nor did it accept, that its letter suggested such a switch without regard for the differences in the way the products should be used and without taking the care that the complainant recommended.

Leo did not accept that its letter suggested a course of action that could be dangerous to patient safety but rather that it suggested a possible alternative treatment and described how to prescribe and use it appropriately.

Both Dovobet and Dononex Ointments were prescription only medicines, prescribable by GPs and appropriately qualified nurse prescribers as well as consultant dermatologists; approximately 97% of prescriptions for both products were written by GPs. It was entirely appropriate to distribute the letter to both GPs and dermatologists. Giving this advice to GPs did not prejudice patient safety but assisted in the correct and appropriate prescribing of products by a group of health professionals who were already the biggest prescribers of these products.

Leo knew of no studies which directly compared the clinical efficacy and cost effectiveness of once daily Dovobet Ointment versus alternative days once-daily Diprosone and Dovonex. The comparative cost-effectiveness claim that Leo made was based upon an indirect comparison used in Leo's submission to the Scottish Medicines Consortium (SMC) and subsequently presented as an abstract at a European dermatology meeting in 2006. A further fuller manuscript had since been published (Bottomley *et al* 2007).

Leo agreed with the complainant that it was important that prescribers were fully aware when prescribing Dovobet that they were using a potent steroid and to be alert to its side effects. This was why its letter and all its promotional material fully complied with the Code and provided the non-proprietary names of the active ingredients adjacent to the brand name and included prescribing information with appropriate precautions, warnings and side effects listed.

The complainant's statement that Dovonex Ointment was withdrawn in April 2007 to coincide with the UK patent expiry was incorrect; Dovonex Ointment was not withdrawn but rather its supply was discontinued, and the patent expired on 14 July 2006.

Leo currently had no specific information about the status of Dovobet or Dovonex Ointment in South America or in the US but would be happy to make enquiries should it be deemed relevant to this complaint.

Leo accepted that the complainant was disappointed by Leo's decision to discontinue supply of Dovonex Ointment and it apologised to him and his patients for any inconvenience this might have caused. However, it gave the required statutory notice period for discontinuing a product and issued a letter to clinicians on 23 February about the discontinuation, two months in advance of actually discontinuing supply to pharmacies.

Leo submitted that its discontinuation of supply of Dovonex Ointment was not a promotional activity but a commercial decision based on prescribing trends, the perceived decline in clinical usefulness compared with other available products, and the need to rationalise its product portfolio in the UK.

Leo had implemented the discontinuation process with consideration for patients and prescribers and had issued its best advice on alternative treatments in response to questions. Although data supported Dovobet as being the most efficacious topical treatment for plaque psoriasis (Douglas *et al*, Guenther *et al* 2002, Kragballe *et al*, van de Kerkhof *et al* 2005), the most pharmacologically similar product to Dovonex Ointment was Dovonex Cream, hence these were the two products recommended as alternatives.

Leo did not believe that its decision to discontinue Dovonex Ointment fell within the scope of the Code and, as such, it did not believe there was a case to answer in this regard. Leo submitted that all its activities in relation to the discontinuation of Dovonex Ointment, including the letter, had been conducted with due regard to, and in conformity with, the requirements of the Code.

PANEL RULING

The Panel noted the complainant's explanation that he had commented on a number of general points by way of background. He did not however make specific allegations about these points. The Panel considered that it had specific allegations about whether the letter implied that patients should be switched from Dovonex Ointment to Dovobet and associated safety issues and the withdrawal of Dovonex.

The Panel noted that the letter stated 'because the clinical usefulness of Dovonex Ointment (calcipotriol 50 micrograms/g) has diminished it is no longer supplied by Leo Pharma in the UK. As a result and in response to enquiries we are continuing to receive we would advise that for the majority of your patients, Dovobet (calcipotriol 50 micrograms/g, betamethasone 0.5 milligrams/g) can replace Dovonex Ointment (calcipotriol 50 micrograms/g)'. There followed discussion of Dovobet's efficacy.

The Panel noted that there were important differences between the products. Dovobet was indicated for the topical treatment of stable plaque psoriasis whereas Dovonex Ointment was indicated more broadly for the topical treatment of plaque psoriasis. Dovobet had a recommended treatment period of four weeks after which repeated treatment could be initiated under medical supervision; there was no recommended treatment period for Dovonex. Dovobet was not recommended for use in children and adolescents below the age of 18 years whereas Dovonex Ointment could be used with care, and with some restrictions as

to maximum weekly dose, in children aged 6 and above. There was limited experience of the use of Dovonex in children under 6 years and a maximum safe dose in that group had not been established. The Dovonex Ointment summary of product characteristics stated that in respect of children clinical experience had shown Dovonex to be safe and effective over eight weeks at a mean dose of 15g per week but with wide variability in dose amongst patients. In addition Dovobet contained a strong, potent topical corticosteroid and had a more extensive list of contraindications and special warnings and precautions for use than Dovonex.

The Panel noted that the letter had a broad circulation including hospital and retail pharmacists, practice nurses, prescribing nurses as well as GPs and consultant dermatologists. The Panel considered that by stating that Dovobet could replace Dovonex Ointment for *the majority* of patients (emphasis added) without making the important differences between the products clear, the letter implied that most patients could be simply switched and that was not necessarily so. There were substantial differences between the products and any switch would have to be conducted with care and on a case by case basis. Dovobet was not recommended for use in patients below the age of 18 years. The reference later in the letter to Dovonex Cream as an option for patients ineligible for treatment with Dovobet did not negate the impression from the preceding paragraphs. The letter was misleading and could not be substantiated in that regard. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted the complainant's allegation that switching from Dovonex to Dovobet, if carried out by those without particular experience in managing psoriasis could, if done without extreme care and case by case selection be dangerous to patient safety and that it was important that prescribers were fully aware that they were using a potent steroid and to be alert to its side effects. The letter referred to 'Dovobet's established and reassuring safety profile'. The Panel noted its ruling above about the impression given by the letter and considered that within the context of a letter which advocated a switch from a non-steroidal treatment to a medicine containing a potent steroid it was important that the material fairly represented Dovobet's risk benefit profile. This was especially important given the wide circulation of the letter in question. The Panel considered that the failure to alert readers to the differing side effect profile of Dovobet versus Dovonex was misleading as alleged; the reference to the prescribing information would not suffice in this regard. A breach of Clause 7.2 was ruled.

The Panel considered that the failure to make it clear that there were important differences between the products, noting in particular the differences in their side effect profiles, meant that the company had failed to maintain high standards. A breach of Clause 9.1 was ruled. On balance the Panel did not consider that in this regard the material brought discredit upon or reduced confidence in the pharmaceutical industry. No breach of Clause 2 was ruled.

The Panel noted the complainant's concern about the withdrawal of Dovonex Ointment from UK supply. The Panel noted that whilst discontinuation of products might give rise to concern and disappointment it was nonetheless a legitimate business activity. The Panel considered that the principle of product discontinuation was *prima facie* outside the scope of the Code. However any reference to product discontinuation within a promotional letter must comply with the Code. The Panel did not consider that the reference to Dovobet's discontinuation within the context of the letter failed to maintain high standards or brought discredit upon or reduced confidence in the pharmaceutical industry as alleged. No breach of Clauses 2 and 9.1 was ruled.

Complaint received	**16 August 2007**
Case completed	**12 October 2007**

CASE AUTH/2036/8/07

VOLUNTARY ADMISSION BY PROCTER & GAMBLE

Promotion of Intrinsa to the public

Procter & Gamble voluntarily admitted promoting Intrinsa (testosterone transdermal patch), a prescription only medicine (POM), to the public. As the matter related to a serious breach of the Code, it was taken up and dealt with as a formal complaint under the Code in accordance with the Constitution and Procedure.

Procter & Gamble stated that an Intrinsa advertisement was placed in the journal 'Wellbeing', which was published in association with the Royal College of Obstetricians and Gynaecologists and Wellbeing of Women, a UK registered charity, in the belief that as the journal was distributed to health professionals, it was solely for their use. However, the health professionals in turn made copies available to patients, typically by placing it in their waiting rooms.

Procter & Gamble and the publisher had agreed to send every recipient of the journal materials to oversticker the Intrinsa advertisement so that patients could no longer see it. The charity had confirmed that it would not distribute any further copies of the journal in the current form.

The Panel considered that from the full title, 'Wellbeing for Women, Mothers & Babies 2007', it should not have been a surprise to Procter & Gamble that the journal was intended for the public. It was not a publication aimed at health professionals. The Panel was extremely concerned that Procter & Gamble had not established the full details about the intended audience and that the advertisement had not been certified. Intrinsia, a POM, had been promoted to the public. A breach of the Code was ruled as acknowledged by Procter & Gamble. High standards had not been maintained and a further breach of the Code was ruled in that regard. The Panel noted Procter & Gamble's actions once the mistake had been discovered including instructions to oversticker the advertisement. However, on balance, the Panel considered that the seriousness of the errors reduced confidence in the pharmaceutical industry and thus a breach of Clause 2 of the Code, which was reserved to indicate particular censure, was ruled.

Procter & Gamble Pharmaceuticals UK Limited voluntarily admitted promoting Intrinsa (testosterone transdermal patch), a prescription only medicine (POM), to the public.

Paragraph 5.4 of the 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 POM to the public was regarded as a serious matter and the Director accordingly decided that the admission must be treated as a complaint.

COMPLAINT

Procter & Gamble stated that an Intrinsa advertisement (ref INT-UK3063) appeared in a journal which might be read by patients. The advertisement, developed for use in journals intended for health professionals, was placed in the June 2007 edition of 'Wellbeing' in the mistaken belief that the journal was intended solely for health professionals; the publisher had stated that the content, including all advertisements, was subject to the editorial control of a senior fellow of the Royal College of Obstetricians and Gynaecologists (RCOG). Indeed, the vast majority of articles were sourced from members of the RCOG. However, although 100,000 copies of the journal were distributed directly to members of the RCOG, they then made it available in their surgeries for patients to read typically by placing it in their waiting rooms.

The journal was produced in association with the RCOG and Wellbeing of Women, a UK registered charity that raised money for research into health issues that solely affected women.

Procter & Gamble agreed with the publisher that it would write to every recipient of the journal (copy letter provided) wherein it would provide materials to oversticker the Intrinsa advertisement so that it was no longer visible to patients. No further distribution would take place by the publisher until the Intrinsa advertisement had been overstickered. Wellbeing of Women had confirmed that it would not distribute any further copies of the journal in the current form.

Procter & Gamble had not been contacted by consumers with regard to this issue. Procter & Gamble was monitoring the situation closely and it would tell any consumer that contacted the company that the advertisement should not have been placed in the journal and that it was doing all it could to prevent any further disclosure.

The publication of the advertisement in such a journal was obviously a very regrettable error; steps had already been taken internally to tighten the approval process for placing print advertisements in journals, and appropriate follow-up action concerning the person involved was being taken.

Procter & Gamble had written similarly to the Medicines and Healthcare products Regulatory Agency (MHRA).

When writing to Procter & Gamble the Authority asked it to respond in relation to Clauses 2, 9.1 and 20.1 of the Code.

RESPONSE

Procter & Gamble fully understood that POMs must not be promoted to the general public, as stated in Clause 20.1 and thus acknowledged that the publication of the advertisement in the journal at issue constituted a breach of Clause 20.1.

Procter & Gamble submitted that regrettably, the advertisement in question was that which was examined by the PMCPA at the audit (Cases AUTH/1902/10/06 and AUTH/1903/10/06) and was found to lack certification by the final signatories. Further actions taken following the findings of the audit would be described in the company's response to the PMCPA audit report.

Procter & Gamble recognised that the special nature of medicines and the professional audience to which the material was directed required that the standards set for the promotion of medicines were higher than those which might be acceptable for general commodity advertising.

Procter & Gamble submitted that the advertisement in question was developed for use in journals intended solely for health professionals and had been pre-vetted by the MHRA. Procter & Gamble therefore believed that it was of the required high standard for advertising to health professionals. As described above, Procter & Gamble had erroneously believed that the publication in question would be distributed only to health professionals.

Procter & Gamble took immediate action with the publisher to determine the facts, and following this, immediately informed both the MHRA and the PMCPA. Procter & Gamble had worked diligently with the publisher to ensure appropriate follow-up action to minimise exposure of this advertisement to the public. Via the publisher, Procter & Gamble had sent correspondence to the same mailing list used for the original journal. The 100,000 copies produced for distribution were actually distributed to approximately 3,500 recipients. Each one received sufficient material to oversticker 30 copies of the advertisement. A free telephone number was also provided in case of questions. Procter & Gamble therefore considered that it had exhibited high standards in handling this situation when it came to its attention and thus denied a breach of Clause 9.1.

Procter & Gamble would never intentionally breach the Code or UK Advertising Regulations, it strove to operate in a responsible, ethical and professional manner as demonstrated by its actions when this error came to its attention. Patient safety and/or public health was not prejudiced at any time by the publication of this advertisement in the journal.

Procter & Gamble acknowledged the seriousness of this case, however given the circumstances, and immediate follow-up actions, it submitted that this did not warrant a breach of Clause 2.

PANEL RULING

The Panel noted that the Intrinsa advertisement had appeared in the Wellbeing journal which was produced in association with the RCOG and Wellbeing of Women, a UK charity that raised money for research into health issues solely effecting women. The full title of the journal was 'Wellbeing for Women, Mothers & Babies 2007'. Procter & Gamble submitted that the publisher had told it that the journal was subject to the editorial control of a senior fellow of the RCOG and had assumed that it was therefore intended solely for a health professional audience. Procter & Gamble had subsequently discovered that once distributed to physicians, they might, in turn, make copies available in their surgeries for patients to read.

The Panel considered that from the title it should not have been a surprise to Procter & Gamble that the journal was intended for the public. It was not a publication aimed at health professionals. The Panel was extremely concerned that Procter & Gamble had not established the full details about the intended audience and that the advertisement had not been certified as required by Clause 14. Intrinsia, a POM had been promoted to the public. A breach of Clause 20.1 was ruled as acknowledged by Procter & Gamble. High standards had not been maintained and a breach of Clause 9.1 was ruled. The Panel noted Procter & Gamble's actions once the mistake had been discovered including instructions to oversticker the advertisement. However, on balance, the Panel considered that the seriousness of the errors reduced confidence in the pharmaceutical industry and thus ruled a breach of Clause 2, which was reserved to indicate particular censure.

Complaint received	**20 August 2007**
Case completed	**19 September 2007**

CASES AUTH/2039/8/07 and AUTH/2040/8/07

PRIMARY CARE TRUST MEDICINES MANAGEMENT PROGRAMME DIRECTOR v BIOGEN IDEC and ELAN PHARMA

Letter about Tysabri

The medicines management programme director at a primary care trust complained about a letter promoting Tysabri (natalizumab) sent by Biogen Idec. Elan Pharma International held the marketing authorization for Tysabri and the letter included Biogen's and Elan's logos on the reverse. The complaint was taken up with both companies.

The letter, headed 'Tysabri is now recommended by [The National Institute for Health and Clinical Excellence] NICE', stated that the product had received a positive final appraisal determination from NICE. The complainant noted that whilst it was very likely that the NICE final appraisal determination would be the guidance to be issued for the NHS, this was not necessarily so. The medicine was not actually recommended for the NHS until the technology appraisal had been issued. The complainant alleged that the heading 'Tysabri is now recommended by NICE' was untrue, misleading and should be withdrawn.

The Panel considered that the heading implied that the recommendation from NICE was final which, when the letter was sent out (14 August), was not so. NICE published the relevant technology appraisal guidance eight days later (22 August). Although the first paragraph of the letter explained that Tysabri had recently received a positive final appraisal determination this did not, in the Panel's view, negate the otherwise false impression of finality given by the heading. In any event the Panel queried how many recipients would appreciate the status of a final appraisal determination.

The Panel considered that when the letter was sent the heading was untrue and misleading as alleged. Breaches of the Code were ruled.

The medicines management programme director at a primary care trust complained about a letter promoting Tysabri (natalizumab) (ref TY00-GBR-22242) sent by Biogen Idec Limited. Elan Pharma International Ltd held the marketing authorization for Tysabri and the letter included Biogen's and Elan's names in logo format on the reverse. The complaint was taken up with both companies.

COMPLAINT

The complainant noted that whilst it was very likely that the NICE final appraisal determination would be the guidance to be issued for the NHS, this was not necessarily so. Also the medicine was not actually recommended for the NHS until the technology appraisal had been issued. The complainant alleged that the heading 'Tysabri is now recommended by NICE' was untrue, misleading and should be withdrawn.

In writing to the companies the Authority drew attention to Clauses 2, 7.2, 7.4 and 9.1 of the Code.

RESPONSE

Biogen Idec and Elan noted that the letter was sent to primary care organisations to inform them of the positive final appraisal determination for natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis from NICE. The heading 'Tysabri is now recommended by NICE' was followed by 'We are pleased to announce that Tysabri has recently received a positive final appraisal determination from NICE. The committee acknowledge that Tysabri is a clinically and cost effective treatment for Highly Active Relapsing Remitting Multiple Sclerosis. This is defined by one or more disabling relapses in one year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI'.

The companies submitted that the claim 'Tysabri is now recommended by NICE' was true. Section 1.1 of the final appraisal determination for natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis stated that:

> 'Natalizumab is recommended as an option for the treatment only of rapidly evolving severe relapsing-remitting multiple sclerosis (RES). RES is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.'

The companies submitted that the claim was also not misleading. The letter cited a publicly available document and clearly indicated that the recommendation was from the NICE final appraisal determination for natalizumab. The letter did not state that Tysabri was recommended for the NHS.

The companies submitted that there was no need for the claim at issue to be withdrawn for the reasons set out above. Not only was natalizumab recommended as a treatment for highly active relapsing-remitting

multiple sclerosis in the final appraisal determination, but it had also been recommended in the NICE technology appraisal guidance 127 (Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis).

The companies submitted that the letter was accurate, balanced, fair, objective and unambiguous, and that the claims therein were capable of substantiation. High standards had been maintained and the companies vehemently rejected any suggestion that the letter discredited or reduced confidence in the pharmaceutical industry. The companies denied breaches of Clauses 2, 7.2, 7.4 or 9.1.

In response to a request for further information the companies submitted that the letter at issue was sent on 14 August 2007; the final appraisal determination was published 3 July 2007 on the NICE website. The NICE Technology Appraisal Guidance 127 was issued 22 August 2007.

The companies submitted that their understanding of the status of a final appraisal determination was that following various rounds of consultations and evaluation of the available evidence, NICE issued its final recommendations in the final appraisal determination which it distributed to all consultees and commentators to the appraisal. Consultees might appeal against the final recommendations and had 15 working days from receipt of the final appraisal determination in which to do so. The final appraisal determination was placed on NICE's website 5 working days after it had been sent to the consultees and commentators. Upon expiry of the appeal period or, if an appeal was lodged, the resolution of the appeal, NICE published its guidance to the NHS. There were only three grounds upon which a consultee might appeal: NICE had failed to act fairly and in accordance with its published procedures; the final appraisal determination was perverse in the light of the evidence submitted or NICE had exceeded its powers.

PANEL RULING

The Panel considered that the letter heading, 'Tysabri is now recommended by NICE', implied that the recommendation from NICE was final which, when the letter was sent out (14 August), was not so. NICE published the relevant technology appraisal guidance eight days later (22 August). Although the first paragraph of the letter explained that Tysabri had recently received a positive final appraisal determination this did not, in the Panel's view, negate the otherwise false impression of finality given by the heading. In any event the Panel queried how many recipients would appreciate the status of a final appraisal determination.

The Panel considered that when the letter was sent the heading was untrue and misleading as alleged. Breaches of Clauses 7.2 and 7.4 were ruled. In the circumstances it did not consider that high standards had not been maintained and no breach of Clause 9.1 was ruled.

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

Complaint received	**24 August 2007**
Case completed	**22 October 2007**

ANONYMOUS EMPLOYEE v SANOFI-AVENTIS

Duties of a representative

An employee of Sanofi-Aventis complained that, as part of a small specialist team, he was being asked to talk about Plavix and off label indications. He had also been asked to gain information about a new competitor product that had not come to the market place. This made him very uncomfortable.

As the complainant was anonymous and non-contactable, and little evidence had been provided, the Panel was extremely cautious in deciding what weight, if any, to attach to the complaint.

The Paned noted that Sanofi-Aventis had denied promoting Plavix for unlicensed indications; scientific advisors, however, were expected to react to unsolicited requests for such information.

The Panel noted that the job description included in the scientific advisor's reference folder was headed 'Scientific Advisor Role Profile-Cardiovascular Business Unit'. It was stated that scientific advisors were critical to the functioning of the cardiovascular business unit by ensuring all scientific information was updated and communicated to health professionals within the NHS in order to maximise business operations. They were also to act as a resource to the sales force; they were to be 'proactive' and a 'self starter'. One of the key objectives and responsibilities was to provide educational information on licensed and unlicensed indications in strict accordance with, *inter alia*, the Code.

Further guidance stated that the role was reactive only when responding to a written request for information about unlicensed use and this point was stressed in the performance metrics. The scientific advisors could work proactively at any other time including contacting customers to introduce themselves and their roles and arranging meetings.

The role was described as predominately customer facing with leads generated by the sales team. Examples given of how the scientific advisors in another business unit supported the business unit included 'Difficult to access customers – Different approach, new and unlicensed data, Investigator initiated trials, audits, advisory boards'.

A separate job description (not included in the folder) described one of the objectives and responsibilities of scientific advisors as management of contact and development of regional key opinion leaders in conjunction with the marketing department.

The Panel was concerned about the arrangements for the scientific advisors and the potential for them to undertake a promotional role. The definition of promotion in the Code included any activity undertaken by a pharmaceutical company which promoted the prescription, supply, sale or administration of its medicines. Examples drawn from other parts of the company appeared to encourage the cardiovascular scientific advisors to use unlicensed data proactively with difficult to access customers.

Although the Panel was very concerned about the documentation, it nonetheless considered there was no evidence on the balance of probabilities that Sanofi-Aventis had promoted Plavix outside its licensed indication as alleged and thus no breach of the Code was ruled.

It was normal commercial practice to seek information about competitor products and this was not in itself a breach of the Code. Sanofi-Aventis had denied activity in this regard other than in accordance with the requirements of the Code.

There being no evidence that Sanofi-Aventis had acted improperly, and no recourse to the complainant for further information the Panel ruled that on the balance of probabilities there had been no breach of the Code.

An employee of Sanofi-Aventis complained about the duties he was being asked to perform.

COMPLAINT

The complainant stated that, as part of a small specialist team he was being asked to talk about Plavix (clopidogrel) and unlicensed indications. He had also been asked to gain information about a competitor product that was not yet marketed. This made him very uncomfortable.

When writing to Sanofi-Aventis, the Authority asked it to respond in relation to Clauses 2, 3.1, 3.2, and 9.1 of the Code and stated it was unclear whether the allegation about gaining information about a competitor product was covered by the Code. This should become clear on receipt of Sanofi-Aventis' response.

RESPONSE

Sanofi-Aventis was disappointed that an employee had directed their concerns to the Authority without having first used the established company policies on whistleblowing, or discussed the matter with any member of Sanofi-Aventis staff.

Sanofi-Aventis emphasised that members of its Plavix promotional teams were not involved in off licence

discussions and knowledge of any contravention of this policy would result in investigation and disciplinary sanctions. Only employees with a non-promotional role namely, medical information officers and medical affairs (including scientific advisors) were permitted to respond to such requests from health professionals on a reactive basis only. The company did not permit the proactive provision of information on unlicensed use of its products outside specialist circumstances eg clinical triallists' meetings, in compliance with the supplementary information to Clause 3.

Sanofi-Aventis explained that it had field-based medical representatives who promoted Plavix in primary and secondary care. However, the company believed that the complainant's reference to a small specialist team referred to either the professional relations executive (PRE) or the scientific advisor (SA) teams. The role and responsibilities of these teams were described below;

The PREs were a field-based promotional team of five who reported to a group product manager based in head office. The PRE team's main role was to interact with local and national opinion leading health professionals supporting their needs through centrally funded programmes and small local projects. They developed local advocacy for company products as well as identified the areas of interest for customers with respect to medical education programmes. The roles and responsibilities were described in the PRE job description which was provided.

The cardiovascular SAs were a non-promotional team of four who reported directly to the cardiovascular medical manager within the medical affairs department. Their roles were cross functional, working with medical information, promotional affairs, clinical operations and commercial on non-promotional scientific activities. Due to the nature of their role, scientific advisors did not use promotional materials. The interaction between scientific advisors and health professionals was reactive to unsolicited requests for scientific or medical information. A full description of their role and responsibilities was included in the job description and the scientific advisors' folder, both of which were provided.

Sanofi-Aventis explained that all of its employees, including members of the PRE and SA teams, had been instructed not to proactively raise any off-licence discussions with health professionals.

Guidance on what to do when a representative received an unsolicited request for off-licence information was given in Code of Practice training during the induction period of a new entrant. If during a discussion with a health professional an employee received an unsolicited request for off-licence information he/she should refer the health professional to a non-promotional member of the company (ie medical information office or a scientific advisor).

Members of the PRE and SA teams were expected to collect information on competitors if the issue was raised by a health professional and then to relay this to the relevant member of the marketing/medical team. This activity was carried out in a manner consistent with the high standards required by the Code and did not involve subterfuge, misrepresentation or disparagement of other companies or their products.

In summary, Sanofi-Aventis stated that it was committed to complying with the Code and upholding high standards required therein; and that all the activities which involved members of the promotional teams were within the licensed indication(s) for the products which they promoted. Sanofi-Aventis therefore did not accept that there had been breaches of the Code as alleged. Specifically, Clause 3 had been adhered to, with clear expectations and briefing as to what actions were permissible in the context of discussions on unlicensed indications of Plavix. High standards had been maintained; the two teams had been briefed on the requirements of the Code and operated within these in both letter and spirit. Collection of competitor information was not prohibited under the Code provided that this did not involve any activity which otherwise contravened its requirements, and again Sanofi-Aventis' briefing did not advocate any such action. Sanofi-Aventis noted that the complainant had offered no evidence to substantiate their vague and general allegations. Taking these factors into consideration, Sanofi-Aventis believed that there had accordingly been no breach of Clause 2, either to reduce confidence in the industry or to bring discredit upon it.

PANEL RULING

The Panel noted that the complainant was anonymous and non-contactable and little evidence had been provided. Thus the Panel was extremely cautious in deciding what weight, if any, to attach to the complaint.

The Panel noted that it had no way of knowing what role the complainant had in Sanofi-Aventis; he had described himself as being 'part of a small specialist team' that talked about Plavix. Sanofi-Aventis had submitted that two roles fitted that description – a scientific advisor or a professional relations executive. The professional relations executive was a promotional role, reporting to a group product manager. Sanofi-Aventis had submitted that all of its employees, including the professional relations executives and the scientific advisors, had been instructed not to proactively raise any off-licence discussions with health professionals. Sanofi-Aventis had denied promoting Plavix for unlicensed indications. The scientific advisors however, were expected to react to unsolicited requests for such information.

The Panel examined the job description for a cardiovascular scientific advisor. There appeared to be two versions, each provided by Sanofi-Aventis. The separate document provided was different to that included in the scientific advisor's reference folder which was headed 'Scientific Advisor Role Profile-

Cardiovascular Business Unit'. The folder stated that scientific advisors were critical to the functioning of the cardiovascular business unit by ensuring all scientific information was updated and communicated to health professionals within the NHS in order for business operations to be maximised. They were also to act as a resource to the sales force.

The folder listed skills and behaviours as 'proactive' and 'self starter'. One of the key objectives and responsibilities was to provide educational information on licensed and unlicensed indications in strict accordance with the Code and Medicines Act. The Panel noted that in order to comply with the Code this could not be a proactive role but would have to be a reactive role. Scientific advisors were to attend the sales conference.

The folder gave some information about the role in relation to the Code. The guidance stated that the role was reactive only when responding to a written request for information about unlicensed use. The scientific advisors could work proactively at any other time including contacting customers to introduce themselves and their roles and arranging meetings.

The performance metrics included 'Exchange of out of licence scientific information - reactive basis only'.

The folder described the role as predominately customer facing with leads generated by the sales team. It also gave examples in the form of slides of how the scientific advisors in another business unit (metabolism) supported the business unit which included 'Difficult to access customers – Different approach, new and unlicensed data, Investigator initiated trials, audits, advisory boards'.

The separate job description described one of the objectives and responsibilities as 'Management of contact and development of regional KOLs [key opinion leaders] in conjunction with the Marketing Department'.

The Panel was concerned about the arrangements for the scientific advisors and the potential for them to undertake a promotional role. The definition of promotion in Clause 1.2 included any activity undertaken by a pharmaceutical company which promoted the prescription, supply, sale or administration of its medicines. The slides could be read such as to imply that the cardiovascular scientific advisors had been encouraged to use unlicensed data proactively with difficult to access customers.

Although the Panel was very concerned about the documentation, it nonetheless considered there was no evidence on the balance of probabilities that Sanofi-Aventis had promoted Plavix outside its licensed indication as alleged and thus no breach of Clauses 3.1 and 3.2 was ruled. The Panel also ruled no breach of Clauses 2 and 9.1.

It was normal commercial practice to seek information about competitor products and this was not in itself a breach of the Code. Sanofi-Aventis had denied activity in this regard other than in accordance with the requirements of the Code.

As the complaint had been submitted anonymously, there could be no recourse to the complainant for further information.

There being no evidence that Sanofi-Aventis had acted improperly, the Panel ruled that on the balance of probabilities there had been no breach of Clause 9.1.

Complaint received	**7 September 2007**
Case completed	**24 September 2007**

CASE AUTH/2044/9/07

CONSULTANT PHYSICIAN V LILLY

Conduct of representative

A consultant physician complained about the conduct of a representative from Lilly. The complainant stated that when the representative came to see him regarding the use of Lilly insulins, he mentioned throughout the course of the conversation that he was under increasing pressure from his managers to try and increase use of Lilly insulin. The exact phrase he used was 'we are basically paying you to use Novo Nordisk's insulins'. He then implied that the funding for an educational post within the local diabetes clinical network was to be reviewed by the Lilly Awards and Grants Committee. He further implied that the managers were not happy with the current situation and that this funding would probably be under threat, since the hospital's use of Lilly insulins had not increased. The complainant pointed out to the representative that the funding for the post had nothing to do with the hospital's use of Lilly insulins. If the representative's comments were a direct threat to cut funding unless the department started to use Lilly's insulins then this was nothing short of blackmail.

The Panel noted that the decision to fund the educational post for two years was approved in May 2006 and the money paid in June that year. Lilly submitted that no member of sales or marketing was involved in the decision process.

Lilly acknowledged that the representative, acting on his own initiative, had behaved inappropriately by linking financial support from Lilly to increased prescribing of Lilly insulins at the hospital. This was totally unacceptable. The Panel ruled breaches of the Code as acknowledged by Lilly.

The Panel noted that the representative had received training on the Code including the requirements on the provision of medical and educational goods and services and the prohibition of linking such services to the promotion of medicines. The representative had not behaved in accordance with Lilly's standard operating procedures and training and had been dismissed. Nonetheless, the Panel considered that high standards had not been maintained. The representative's behaviour had brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel ruled breaches of the Code including Clause 2.

The Panel decided that as the representative was acting outside the company's instructions it would not report Lilly to the Code of Practice Appeal Board.

A consultant physician complained about the conduct of a representative from Eli Lilly and Company Limited.

COMPLAINT

The complainant stated that when the representative came to see him recently regarding the use of Lilly insulins, he mentioned throughout the course of the conversation that he was under increasing pressure from his managers to try and increase use of Lilly insulin. The exact phrase he used was 'we are basically paying you to use Novo Nordisk's insulins'. He then implied that the funding for an educational post within the local diabetes clinical network was to be reviewed by the Lilly Awards and Grants Committee. He further implied that the managers were not happy with the current situation and that this funding would probably be under threat, since the hospital's use of Lilly insulins had not increased. The complainant pointed out to the representative that the funding of the post had nothing to do with the hospital's use of Lilly insulins. The complainant also told the representative in no uncertain words that he felt this was a direct threat and he was not very happy about it.

The complainant had now had time to consider the situation and had informed Lilly that the representative was no longer welcome in the diabetes department or hospital. The complainant had also informed the representative that what he did was against ABPI regulations and was tantamount to a threat if not blackmail. The complainant also emphasised to the representative that the hospital's plan had always been for the person appointed to the educational post to provide a 9-month review report on the work done so far and this would form the basis of a review into funding for the following year. The complainant had also emphasised that this had nothing to do with clinical care in the diabetes clinics.

The complainant sought some clarification from Lilly as to whether this was a direct threat to cut funding if the department did not start using Lilly's insulins. If it was a direct threat then this was nothing short of blackmail.

When writing to Lilly, the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2, 18.1 and 18.4 of the Code.

RESPONSE

Lilly regretted that, despite training to the contrary, the representative had used the history of an unconditional grant to unfairly pressurise the complainant (breach of Clauses 18.2 and 18.4). The representative was acting on his own without the explicit or implicit approval of the management; the investigation found that no instructions, either verbal or written, were issued directing the representative to link the provision of financial support from Lilly to an increase in

prescriptions at the hospital. The findings of the investigation resulted in the representative being immediately dismissed.

Lilly reassured the Authority that the actions of this one representative did not mirror the values of the company. Lilly operated strict procedures to ensure compliance with local laws, the Code and the Foreign Corrupt Practice Act (as a US subsidiary). Lilly considered representative training to be at the core of the business in line with the Code.

All requests made to Lilly for financial support were managed by a Grants and Donations Committee, in accordance with Lilly's standard operating procedure (SOP) (copy provided). This committee was comprised of senior personnel from medical, legal and corporate affairs and the decision to grant any funding rested entirely with this committee. No member of sales or marketing formed part of that committee. All requests for funding had to be from an institution or organisation, substantiated by written documentation and unrelated to the prescribing, purchasing, registration or reimbursement of Lilly medicines. Factors considered in the decision to fund a request included the potential benefits to patient care, to the NHS and NHS staff or to the local community.

The request for funding referred to by the complainant was initiated by his colleague in May 2006. Lilly received a detailed application requesting funding for the post (details of the cost were provided). The request was approved by the Grants and Donations Committee in early May 2006. Given the size of the funding, in accordance with Lilly's SOPs, it required the additional approval of its general manager which it received in May 2006. No member of sales or marketing was included in this decision making process. As part of the procedure and prior to the release of any funds, the funding applicant replied to Lilly indicating that he understood that Lilly's funding did not imply an obligation regarding the prescribing, dispensing, registration or purchasing of Lilly products. A cheque was issued in June 2006.

The representative in question had been employed by Lilly since the early 1980s and had passed the medical representatives' examination. He completed mandatory training on the grants and donations procedure in January 2006, March 2007 and again July 2007. The content of each training session was provided and each training course emphasised that the decision to provide a grant/donation must be unrelated to the prescribing, purchasing, registration or reimbursement of any Lilly product. Lilly employees worldwide must also comply with the Lilly Code of Business Conduct (Red Book) and training was mandated annually. This further emphasised that all employees must act ethically and in a manner beyond reproach. The Red Book training record for the representative was complete for the past number of years.

Lilly believed that all reasonable precautions had been taken to ensure compliance with the local regulations and deeply regretted that despite such extensive training, this incident had occurred. The conduct of this one representative had embarrassed Lilly (breach of Clause 15.2) and for this Lilly could only apologise both to the complainant and to the Authority. Lilly re-emphasised that the actions of this individual were contrary to the company's ethos and values. Lilly strove to ensure that all its dealings with health professionals were ethical, compliant with the Code and of the highest professional standards and Lilly therefore did not believe this isolated act brought discredit to the pharmaceutical industry at large (Clause 2).

PANEL RULING

The Panel noted that the decision to fund the educational post for two years was approved in May 2006 and the money paid in June that year. Lilly submitted that no member of sales or marketing was involved in the decision process.

The Panel noted that Lilly acknowledged that the representative, acting on his own initiative, had behaved inappropriately by linking financial support from Lilly to increased prescribing of Lilly insulins at the hospital. This was totally unacceptable. The Panel ruled breaches of Clauses 18.1, 18.4 and 15.2 as acknowledged by Lilly.

The Panel noted that the representative had received training on the Code including the requirements in Clause 18 on the provision of medical and educational goods and services and the prohibition of linking such services to the promotion of medicines. The representative had not behaved in accordance with the SOPs and training and had been dismissed. Nonetheless, the Panel considered that high standards had not been maintained. The representative's behaviour had brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel ruled breaches of Clauses 9.1 and 2.

The Panel decided that as the representative was acting outside the company's instructions it would not report Lilly to the Code of Practice Appeal Board.

Complaint received	**10 September 2007**
Case completed	**26 October 2007**

PRIMARY CARE TRUST DIRECTOR OF STANDARDS v JANSSEN-CILAG

Invega journal advertisement

The director of standards at a primary care trust alleged that an advertisement for Invega (paliperidone prolonged release tablets) placed by Janssen-Cilag in Doctor, breached the Code in its unacceptable use of naked people and sexual imagery. Invega was indicated for the treatment of schizophrenia.

The Panel noted that the advertisement featured a photograph of a young naked woman who was in the process of shedding her skin. The woman was positioned such that her torso was not completely visible. The Panel did not consider that in the context of the advertisement, noting in this regard the claim 'For the person within', the photograph was unacceptable in relation to the prohibition on the use of naked people or sexual imagery to attract attention. The Panel did not consider that the majority of health professionals would be offended by the advertisement. The Panel ruled no breach of the Code.

The director of standards at a primary care trust complained about an advertisement (ref IBE/07-0052) for Invega (paliperidone prolonged release tablets) placed by Janssen-Cilag Ltd in Doctor, 18 September. Invega was indicated for the treatment of schizophrenia.

COMPLAINT

The complainant alleged that the advertisement breached Clause 9 of the Code in its unacceptable use of naked people and sexual imagery.

When writing to Janssen-Cilag, the Authority asked it to respond in relation to Clauses 9.1 and 9.2 in particular.

RESPONSE

Janssen-Cilag refuted breaches of Clauses 9.1 and 9.2 as it considered that high standards had been maintained and that the advertisement did not depict naked or partially naked people for 'the purpose of attracting attention to the material or the use of sexual imagery for that purpose'.

The depiction of a woman shedding her skin was a metaphor for the potential effect of this antipsychotic and the focus was on the efficacy of the medicine and the potential improvement of the patient's mental state subsequent to taking Invega. This was linked to the strapline 'For the person within'. The strapline further explained the image and it was important to view the piece in its entirety. The woman was not depicted clothed since an essential element of the concept was of 'shedding skin' to reveal 'the person within'. This image was not designed to be in any way sexual in nature and Janssen-Cilag was convinced that most health professionals would not find the image offensive or sexual in nature. Janssen-Cilag also contended that the image was not unsuited to the concepts of improving a patient's well-being within a psychiatric context and hence did not believe that its format or suitability were in breach of Clause 9.

Janssen-Cilag, of course, would not wish to offend health professionals, and as such the image used in the advertisement had undergone market research testing, involving 43 psychiatrists, during the various stages of its development. The advertisement had also been pre-vetted by the Medicines and Healthcare products Regulatory Agency (MHRA); no issues of unsuitability of the image or taste were raised.

Janssen-Cilag believed that the diligence undertaken during the development of this concept, which convinced it that the advertisement would not be likely to cause offence to the majority of health professionals, such that it would be consistent with the requirements of Clause 9.2, also demonstrated awareness of the requirements of Clause 9.1 and Janssen-Cilag contended that high standards had been maintained. While recognising differences in personal taste, the company was satisfied that the vast majority of health professionals viewing this advertisement would not find it offensive or sexual in nature.

PANEL RULING

The Panel noted that the advertisement featured a photograph of a young naked woman who was in the process of shedding her skin. The woman was positioned such that her torso was not completely visible. The Panel did not consider that in the context of the advertisement, noting in this regard the claim 'For the person within', the photograph was unacceptable in relation to the prohibition on the use of naked people or sexual imagery to attract attention. The Panel did not consider that the majority of health professionals would be offended by the advertisement. The Panel ruled no breach of Clauses 9.1 and 9.2.

Complaint received	26 September 2007
Case completed	29 October 2007

CASE AUTH/2048/9/07

VOLUNTARY ADMISSION BY GRÜNENTHAL

Breach of undertaking

Grünenthal voluntarily admitted that it had breached the undertaking and assurance in relation to a journal advertisement for Versatis (lidocaine medicated plaster) which it had given in Case AUTH/1960/2/07.

When Grünenthal undertook not to use the advertisement at issue in Case AUTH/1960/2/07 it so advised its advertising agency and asked it to put in place a number of actions. It instructed Pulse by email to destroy old electronic copies of the advertisement and replace them with a new version. The new pdf was attached to an email which stated 'The easiest way to confirm the new copy, is by its revised headline. This now says "New for the burning, shooting stabbing pains of post-herpetic neuralgia"'. This email was followed up by a hard copy in the post.

Following these procedures the correct advisement was run in the 26 April edition of Pulse and on three subsequent occasions.

Investigations showed that Pulse did not destroy the old pdf. It was the publisher's policy to check the content of the advertisement before sending it to print but on this occasion its internal procedures were not followed. This had been confirmed in writing by the head of client services at the publishers.

It therefore appeared that the undertaking had been breached because the publisher had not followed Grünenthal's explicit instructions to destroy the old material. Nor had it followed its own internal processes to check the print version was the correct one to use. It was difficult to assess how Grünenthal could have anticipated this outcome when Pulse had previously and regularly published the correct version of the advertisement. In support of its internal processes Grünenthal noted that several journals including the BMJ and Practitioner had correctly followed its procedures and published revised versions of the advertisement.

Paragraph 5.4 of the Authority's Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. A breach of undertaking was regarded as a serious matter and the admission was accordingly treated as a complaint.

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

The Panel noted that in Case AUTH/1960/2/07 it had ruled that an advertisement for Versatis was in breach of the Code. The advertisement had featured the claim 'New for burning, shooting, stabbing, pains'. Grünenthal provided the requisite undertaking on 3 April 2007. Pulse had published the updated advertisement in April and May but had reverted to the previous advertisement for its 13 and 20 September 2007 editions.

The Panel noted that correspondence from Grünenthal clearly instructed Pulse to destroy old versions of the Versatis advertisement. The company had explained that the way to differentiate the new advertisement from the old was that the new advertisement stated 'New for the burning, shooting, stabbing pains of post-herpetic neuralgia'. In that regard, given the similarity between the old and new claim, it might have been helpful to emphasize the need for 'post-herpetic neuralgia' to be included in the headline. There was no mention in the correspondence that the claim had had to be revised following a ruling of a breach of the Code and therefore the importance of complying with Grünenthal's instruction was not made clear to the publishers. Grünenthal had not asked the publishers to confirm that the old version of the advertisement had been destroyed. The Panel considered that Grünenthal had taken steps to comply with its undertaking and although its instructions to the publisher could have been more explicit it had, nonetheless, been very badly let down by Pulse. The Panel ruled a breach of the Code as Pulse's failure to comply with Grünenthal's instructions meant that Grünenthal had breached its undertaking. In the circumstances the Panel did not consider that Grünenthal had on balance failed to maintain high standards or that it had brought discredit upon, or reduced confidence in, the industry.

Grünenthal Ltd voluntarily admitted that it had breached the undertaking and assurance in relation to a journal advertisement for Versatis (lidocaine medicated plaster) which it had given in Case AUTH/1960/2/07.

COMPLAINT

Grünenthal explained that in March 2007 a Versatis advertisement was found in breach of Clause 3.2. In response to this Grünenthal provided an undertaking on 2 April and put a number of procedures in place to ensure the advertisement was withdrawn. Unfortunately Grünenthal noted that the advertisement had appeared in Pulse, 13 September. It

immediately notified the publisher to ensure no further prints would be made. However, it was too late to prevent Pulse from making the same mistake in the 20 September edition. Grünenthal regarded a breach of undertaking as a very serious matter and had dealt with this issue both promptly and rigorously to identify the causal factors.

Following Case AUTH/1960/2/07, Grünenthal undertook not to use the advertisement again. The advertising agency was so informed and asked to put in place a number of actions. It emailed Pulse with the instruction to destroy old copies of the advertisement (pdf version) and replace with a new pdf version. The new pdf was attached to the email and a clarifying statement was also given to ensure the publisher could identify the new advertisement. The statement was 'The easiest way to confirm the new copy, is by its revised headline. This now says "New for the burning, shooting stabbing pains of post-herpetic neuralgia"'. This email was followed up by a hard copy in the post.

Following these procedures the correct advisement was run in the 26 April edition of Pulse and on three subsequent occasions.

Investigations showed that Pulse did not destroy the pdf. It was the publisher's policy to check the content of the advertisement before sending it to print but on this occasion its internal procedures were not followed. This had been confirmed in writing by the head of client services at the publishers.

It therefore appeared that the undertaking had been breached because the publisher had not followed Grünenthal's explicit instructions to destroy the old material. Nor had it followed its own internal processes to check the print version was the correct one to use. It was difficult to assess how Grünenthal could have anticipated this outcome when Pulse had previously and regularly published the correct version of the advertisement. In support of its internal processes Grünenthal noted that several journals including the BMJ and Practitioner had correctly followed its procedures and published revised versions of the advertisement.

Grünenthal was disappointed to have to make this voluntary admission believing that it had operated in every way to comply with the undertaking, demonstrated by the successful nature of its actions. Grünenthal had acted promptly regarding this issue, in a timely and professional manner, in keeping with its company ethos to uphold the industry's reputation at all times.

Paragraph 5.4 of the Authority's Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. A breach of undertaking was regarded as a serious matter and the admission was accordingly treated as a complaint.

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

RESPONSE

Grünenthal stated that having signed an undertaking and in order to ensure high standards were maintained at all times, it had in place a procedure which was implemented immediately to withdraw the Versatis advertisement at issue in Case AUTH/1960/2/07. The aim was to inform its agencies and provide clear instructions to ensure that it complied with its undertaking. In this case the objective was to ensure no further publication of the advertisement found to be in breach. The events following the undertaking relevant to this case were as follows:

Grünenthal informed agencies of undertaking (28 March 2007).

Creative agency sent revised advertisement (electronically and in hard copy) to publisher with instructions to destroy old advertisements (18 April 2007– copies provided).

Publisher printed new advertisement in Pulse (editions 26 April and 3, 17 and 24 May 2007).

Grünenthal received positive endorsement that the procedure had worked effectively when the correct advertisement was published in Pulse (and other journals) one week later.

As noted above it appeared that Pulse did not destroy the pdf and thus this breach of undertaking had arisen due to the publisher's failure to follow Grünenthal's explicit instructions to destroy the old material and to follow its own internal processes and check the print version was the correct one to use. In essence this was a result of human error on the part of an employee of Pulse for which the publishers took full responsibility.

It was difficult to assess how Grünenthal could have anticipated this outcome when Pulse had previously and regularly published the correct version of the advertisement. Grünenthal reiterated that several journals including the BMJ and Practitioner had correctly followed its procedures and published revised versions of the advertisement. Grünenthal believed it had good procedures in place which it had implemented correctly. It was difficult to see how they could be improved to completely avoid human error.

Grünenthal believed the facts of the case demonstrated that it had rigorous procedures in place to ensure it complied with the demands of the Code and had not brought discredit to the industry.

The advertisement in breach was effectively withdrawn. This was evidenced by the Versatis campaign running effectively and within the Code for five months from the ruling prior to the Pulse publication.

PANEL RULING

The Panel considered that an undertaking was an

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

The Panel noted that in Case AUTH/1960/2/07 it had ruled that an advertisement for Versatis was in breach of the Code. The advertisement had featured the claim 'New for burning, shooting, stabbing, pains'. Grünenthal provided the requisite undertaking on 3 April 2007. Pulse had published the updated advertisement in April and May but had reverted to the previous advertisement for its 13 and 20 September 2007 editions.

The Panel noted that correspondence from Grünenthal clearly instructed Pulse to destroy old versions of the Versatis advertisement. The company had explained that the way to differentiate the new advertisement from the old was that the new advertisement stated 'New for the burning, shooting, stabbing pains of post-herpetic neuralgia'. In that regard, given the similarity between the old and new claim, it might have been helpful to emphasize the need for 'post-herpetic neuralgia' to be included in the headline. There was no mention in the correspondence that the claim had had to be revised following a ruling of a breach of the Code and therefore the importance of complying with Grünenthal's instruction was not made clear to the publishers. Grünenthal had not asked the publishers to confirm that the old version of the advertisement had been destroyed.

The Panel considered that Grünenthal had taken steps to comply with its undertaking and although its instructions to the publisher could have been more explicit it had, nonetheless, been very badly let down by Pulse. The Panel ruled a breach of Clause 22 as Pulse's failure to comply with Grünenthal's instructions meant that Grünenthal had breached its undertaking. In the circumstances the Panel did not consider that Grünenthal had on balance failed to maintain high standards. No breach of Clause 9.1 was ruled. The Panel did not consider that Grünenthal had brought discredit upon, or reduced confidence in, the industry and thus no breach of Clause 2 was ruled.

Complaint received	**27 September 2007**
Case completed	**25 October 2007**

VOLUNTARY ADMISSION BY GLAXOSMITHKLINE and ROCHE

Breaches of undertakings

GlaxoSmithKline and Roche voluntarily admitted that they had breached undertakings given in Cases AUTH/1971/3/07 and AUTH/1972/3/07 in relation to the promotion of Bonviva (ibandronic acid). The companies had, in good faith, given an undertaking not to use the claim 'Building Bones' after June 13.

In line with standard operating procedures (SOPs), the sales force was told to withdraw all promotional materials with the 'Building Bones' claim and return them to head office for destruction. Similarly all agencies and publishing companies were told to withdraw, destroy and to stop using the only Bonviva advertisement running at that time which carried the claim.

Email confirmation of the above actions was received from all the relevant agencies and publishing companies. Roche and GlaxoSmithKline were satisfied that all third parties had taken all steps necessary to prevent the claim being used. The companies were thus extremely surprised and disappointed to find an advertisement containing the 'Building Bones' claim in the 20 September issue of Pulse.

Initial investigations revealed that the publishing company for Pulse had published this advertisement despite confirmation that it had withdrawn, destroyed and was to stop using existing copies of the Bonviva advertisement containing the claim.

Roche and GlaxoSmithKline deeply regretted that this situation had occurred. The companies acknowledged that this had placed them in breach of the undertaking and thus in breach of the Code.

Paragraph 5.4 of the Authority's Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. A breach of undertaking was regarded as a serious matter and the admission was accordingly treated as a complaint.

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

The Panel noted that in Cases AUTH/1971/3/07 and AUTH/1972/3/07 the claim 'Building Bones' for Bonviva was ruled in breach of the Code. Roche and GlaxoSmithKline provided the requisite undertakings in June 2007 stating that the final use of, *inter alia*, the journal advertisement was 13 June 2007. Pulse had re-published the advertisement on 20 September 2007.

The Panel noted that an email from a senior media buyer to the publishers of Pulse gave clear instructions not to run the latest Bonviva copy due to required amendments to bring it in line with ABPI guidelines and to destroy existing copy and confirm receipt of the email. New copy was being developed and would be distributed as soon as possible. The publishers of Pulse confirmed that the email had been sent to the production department and existing copy would no longer be used. It did not, however, confirm that relevant copy would be destroyed, as requested. Most other recipients of the email referred to destruction of the material in their response. Following investigation with the publishers of Pulse it appeared that the advertisement was removed from the last 3-4 insertion files but copy remained on the system for a year. The procedure was that a note was put on the file clearly highlighting that the copy was not to be used again. In this instance the production contact had looked back several months beyond the last Bonviva insertion to repeat copy rather than chasing new artwork.

The Panel considered that GlaxoSmithKline and Roche had taken all possible steps to comply with its undertaking. The companies had been badly let down by Pulse. The Panel had no option but to rule a breach of the Code as Pulse's failure to comply with the instructions meant that GlaxoSmithKline and Roche had breached their undertakings as acknowledged by both companies. In the circumstances the Panel did not consider that GlaxoSmithKline and Roche had failed to maintain high standards or that they had brought discredit upon, or reduced confidence in, the industry.

GlaxoSmithKline UK Ltd and Roche Products Limited voluntarily admitted that they had breached undertakings and assurances that they had given in Cases AUTH/1971/3/07 and AUTH/1972/3/07 in relation to the promotion of Bonviva (ibandronic acid).

COMPLAINT

Writing on behalf of both companies, GlaxoSmithKline advised the Authority of a likely breach of the Code in relation to Cases AUTH/1971/3/07 and AUTH/1972/3/07.

GlaxoSmithKline explained that the companies had unsuccessfully appealed the use of the strapline,

'Building Bones', in the above cases and accepted the Code of Practice Appeal Board's rulings of breaches of Clauses 7.2 and 7.4. The undertaking stated that the claim would not be used after 13 June. Both Roche and GlaxoSmithKline took an undertaking extremely seriously and took all necessary steps to ensure that the claim would not be used again in any form.

In line with company standard operating procedures (SOPs), the sales force was told to withdraw all promotional materials with the claim and these materials were returned to head office and destroyed. Similarly all agencies and publishing companies were told to withdraw, destroy and to stop using the only Bonviva advertisement running at that time which carried the 'Building Bones' claim.

Email confirmation of the above actions was received from all the relevant agencies and publishing companies. Roche and GlaxoSmithKline were satisfied that all third parties had confirmed to them and taken all steps necessary to prevent this claim from being used.

Given the above, the companies were thus extremely surprised and disappointed to find an advertisement containing the 'Building Bones' claim in the 20 September issue of Pulse. An investigation was initiated on the same day to find the source of the advertisement.

Initial investigations discovered that the publishing company for Pulse had published this advertisement despite confirmation that it had withdrawn, destroyed and was to stop using existing copies of the Bonviva advertisement containing the 'Building Bones' claim. Further investigations with the publishers to better understand why the material was not destroyed as requested were ongoing.

Roche and GlaxoSmithKline deeply regretted that this situation had occurred through the inadvertent use of an old advertisement by a publishing company despite Roche and GlaxoSmithKline acting in line with company SOPs and confirming with each supplier that the required actions had been taken. The companies acknowledged that this had placed them in breach of the undertaking signed in good faith and thus in breach of the Code.

Paragraph 5.4 of the Authority's Constitution and Procedure provided that the Director should treat a voluntary admission as a complaint if it related to a potentially serious breach of the Code or if the company failed to take appropriate action to address the matter. A breach of undertaking was regarded as a serious matter and the admission was accordingly treated as a complaint.

When writing to GlaxoSmithKline and Roche, the Authority asked them to respond in relation to Clauses 2, 9.1 and 22 of the Code.

RESPONSE

On behalf of both companies, GlaxoSmithKline reiterated the course of events as detailed above.

GlaxoSmithKline submitted that, as previously mentioned, the media agency had received emails from all the publishing companies to withdraw, destroy and stop using the only Bonviva advertisement which contained the 'Building Bones' claim at that time. This included confirmation from Pulse's publishers on 26 May.

Investigation within the publishing company revealed a fault in its publication process. It was found that removing the copy of the advertisement from records erased it from the last three or four insertion files. The copy of the advertisement did not leave the system for a year. A note was also put on the copy file highlighting that it should never be used again.

However, on this occasion, the production contact for the publishing company had looked back several months beyond the last Bonviva advertisement insertion to repeat the copy of their own accord in contravention of the explicit instructions given. There was no instruction to do this from either Roche or GlaxoSmithKline. As a result, the Bonviva advertisement with the 'Building Bones' claim was published in the 20 September issue of Pulse.

The publishers were deeply apologetic for the error and the fact that this had caused Roche and GlaxoSmithKline to be in breach of their undertakings. The companies were equally disturbed that, despite a written guarantee from the publishing company, this had occurred. The publishing company had since taken steps to ensure that such a mistake would not occur again.

Roche and GlaxoSmithKline deeply regretted that this situation had occurred through the inadvertent use of an old advertisement by a publishing company, which had previously confirmed by email that the advertisement had been withdrawn, destroyed and stopped from being used.

Roche and GlaxoSmithKline had taken extensive steps to prevent this from happening, acting in line with company procedures and receiving written confirmation from each supplier that the required actions had been taken.

Roche and GlaxoSmithKline were confident that they had a robust system in place to withdraw promotional material and had demonstrated this in the course of this response. Nevertheless, both companies recognised that under the Code they were responsible for the actions of their agents. As such they regretfully admitted a breach of Clause 22 as an advertisement previously ruled in breach of the Code had reappeared. This was despite compliance with their own SOPs which included the need for 100% confirmation from all parties that they had taken the required actions to prevent this occurring.

Given that the publishing company had admitted that the failing was entirely its and had taken remedial action to prevent recurrences, and that neither Roche nor GlaxoSmithKline procedures were at fault in this

case, they did not believe that they had incurred breaches of Clauses 9.1 or 2.

PANEL RULING

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

The Panel noted that in Cases AUTH/1971/3/07 and AUTH/1972/3/07 the Appeal Board had ruled that the claim 'Building Bones' for Bonviva was in breach of the Code. Roche and GlaxoSmithKline provided the requisite undertakings in June 2007 stating that the final use of, *inter alia*, the journal advertisement was 13 June 2007. Pulse had re-published the advertisement on 20 September 2007.

The Panel noted that an email from a senior media buyer to the publishers of Pulse gave clear instructions not to run the latest Bonviva copy due to required amendments to bring it in line with ABPI guidelines and to destroy existing copy and confirm receipt of the email. New copy was being developed and would be distributed as soon as possible. The publishers confirmed that the email had been sent to the production department and existing copy would no longer be used. It did not, however, confirm that relevant copy would be destroyed, as requested. Most other recipients of the email referred to destruction of the material in their response. Following investigation with the publishers it appeared that the advertisement was removed from the last 3-4 insertion files but copy remained on the system for a year. The procedure was that a note was put on the file clearly highlighting that the copy was not to be used again. In this instance the production contact had looked back several months beyond the last Bonviva insertion to repeat copy rather than chasing new artwork.

The Panel considered that GlaxoSmithKline and Roche had taken all possible steps to comply with its undertaking. The companies had been badly let down by Pulse. The Panel had no option but to rule a breach of Clause 22 as Pulse's failure to comply with the instructions meant that GlaxoSmithKline and Roche had breached their undertakings as acknowledged by both companies. In the circumstances the Panel did not consider that GlaxoSmithKline and Roche had failed to maintain high standards or that they had brought discredit upon, or reduced confidence in, the industry. Thus no breach of Clauses 2 and 9.1 was ruled.

Complaint received	**27 September 2007**
Cases completed	
Case AUTH/2049/9/07	**25 October 2007**
Case AUTH/2050/9/07	**29 October 2007**

CODE OF PRACTICE REVIEW – NOVEMBER 2007

Cases in which a breach of the Code was ruled are indexed in **bold type.**

1902/10/06 and 1903/10/06	**Employee v Sanofi-Aventis and Procter & Gamble**	**Osteoporosis audit programmes**	**Breaches Clauses 2, and 18.1** **Audits required by Appeal Board** **1903/10/06 Further Audit in January 2008 required by Appeal Board.**	**Appeal by respondents** **Report from Panel to Appeal Board**	**Page 3**
1971/3/07 and 1972/3/07	**Servier Laboratories v Roche and GlaxoSmithKline**	**Promotion of Bonviva**	**Breaches Clauses 7.2 and 7.4**	**Appeal by respondents**	**Page 35**
1977/3/07	**Pfizer v AstraZeneca**	**Statin documents**	**Breach Clause 2** **Two Breaches Clause 4.1** **Eight Breaches Clause 7.2** **Two Breaches Clause 7.3** **Breaches Clauses 7.10, 8.1 9.1 and 9.10** **Two Breaches Clause 10.1** **Public reprimand by Appeal Board** **Audit required by Appeal Board**	**Report from Panel to Appeal Board** **Suspension of PCT prescribing guideline document pending final outcome of the case required by Panel**	**Page 41**
1980/3/07 and 1983/3/07	**Media/Director and Anonymous v Sanofi Pasteur MSD**	**Promotion of Gardasil and arrangements for a meeting**	**Breaches Clauses 9.1, 19.1 and 19.3**	**No appeal**	**Page 55**
1992/4/07	Pharmacist Practitioner v Sanofi-Aventis	Conduct of representative	No breach	No appeal	Page 62
1997/5/07	GlaxoSmithKline v Takeda	Actos Mailing	No breach	Appeal by respondent	Page 68
2006/5/07	**Pharmacist Practitoner v GlaxoSmithKline**	**Promotion of Seretide**	**Breaches Clauses 7.2 and 7.4**	**No appeal**	**Page 73**
2009/6/07	Anonymous v Flynn Pharma	Promotion of Medikinet	No breach	No appeal	Page 75
2010/6/07	General Practitioner v Sanofi-Aventis	Promotion of Acomplia	No breach	No appeal	Page 78
2011/6/07	Primary Care Trust Chief Pharmacist v Takeda	Promotion of Actos and Competact	No breach	No appeal	Page 80
2012/6/07	**GlaxoSmithKline v Takeda**	**Competact mailer**	**Breaches Clauses 2, 7.2, 7.3 and 9.1**	**No appeal**	**Page 85**
2014/6/07	Consultant in Public Health v Pfizer	Promotion of Champix	No Breach	No appeal	Page 89

2015/7/07	**Lilly v Bayer Schering Pharma**	**Promotion of Levitra**	**Three breaches Clause 7.2 Breaches Clauses 7.3 and 7.4**	**No appeal**	**Page 91**
2016/7/07	**Novartis v Bristol-Myers Squibb**	**Sprycel leavepiece**	**Two breaches Clause 7.2**	**No appeal**	**Page 94**
2019/7/07	**Leo Pharma v Galderma**	**Silkis 'Dear Doctor' letter**	**Two breaches Clause 7.2 Two breaches Clause 7.4 Breach Clause 7.5**	**No appeal**	**Page 99**
2021/7/07 and 2024/7/07	**Health Boards v Lundbeck**	**Letter about Cipralex**	**Breaches Clauses 7.2, 7.4 and 9.1**	**No appeal**	**Page 103**
2022/7/07	**General Practitioner v Beacon**	**Episenta unsolicited email**	**Breach Clause 9.9**	**No appeal**	**Page 105**
2023/7/07	**Teaching Primary Care Trust Pharmacist v Pfizer**	**Champix GP Referral Aid**	**Breaches Clauses 2, 9.1 and 7.10 Recovery of item required by Appeal Board**	**Appeal by respondent Report from Panel to Appeal Board Suspension of item at issue pending the final outcome of the case required by Panel**	**Page 108**
2025/7/07	**General Practitioner v Napp**	**Conduct of representative**	**Breaches Clauses 9.1 and 15.2**	**No appeal**	**Page 115**
2027/7/07	**Member of the Public v GlaxoSmithKline**	**Conduct of representative**	**No breach**	**No appeal**	**Page 118**
2029/7/07 and 2030/7/07	**Myocardial infarction National Audit Project v Sanofi-Aventis and Bristol-Myers Squibb**	**Sponsored meetings**	**Breach Clause 9.1**	**No appeal**	**Page 120**
2031/8/07	Formulary Manager v AstraZeneca	Conduct of a representative	No breach	No appeal	Page 125
2034/8/07	**Medicines and Healthcare Products Regulatory Agency v Recordati**	**Tradorec XL leavepiece**	**Breach Clause 9.5**	**No appeal**	**Page 128**
2035/8/07	**Consultant Dermatologist v Leo Pharma**	**Dovabet 'Dear Doctor' letter**	**Two breaches Clause 7.2 Breaches Clauses 7.4 and 9.1**	**No appeal**	**Page 130**
2036/8/07	**Voluntary Admission by Procter & Gamble**	**Promotion of Intrinsa to the public**	**Breaches Clauses 2, 9.1 and 20.1**	**No appeal**	**Page 135**

2039/8/07 and 2040/8/07	**Primary Care Trust Medicines Management Programme Director v Biogen Idec and Elan Pharma**	**Letter about Tysabri**	**Breaches Clauses 7.2 and 7.4**	**No appeal**	**Page 137**
2043/8/07	Anonymous Employee v Sanofi-Aventis	Duties of a representative	No breach	No appeal	Page 139
2044/9/07	**Consultant Physician v Lilly**	**Conduct of representative**	**Breaches Clauses 2, 9.1, 15.2, 18.1 and 18.4**	**No appeal**	**Page 142**
2047/9/07	Primary Care Trust Director of Standards v Janssen-Cilag	Invega journal advertisement	No breach	No appeal	Page 144
2048/9/07	**Voluntary Admission by Grünenthal**	**Breach of undertaking**	**Breach Clause 22**	**No appeal**	**Page 145**
2049/9/07 and 2050/9/07	**Voluntary Admission by GlaxoSmithKline and Roche**	**Breaches of undertakings**	**Breach Clause 22**	**No appeal**	**Page 148**

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
- 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
- the provision of information to the public either directly or indirectly, including by means of the Internet
- relationships with patient organisations.

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.