PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 45 AUGUST 2004

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

Annual Report for 2003

The Annual Report of the Prescription Medicines Code of Practice Authority for 2003 has now been published and copies have been sent to all who are on the mailing list for the Code of Practice Review. Further copies are available on request.

As previously reported in the Review, there were 131 complaints in 2003 as compared with 127 in 2002. There were 138 complaints in 2001.

The 131 complaints in 2003 gave rise to 122 cases, the same as in 2002. The reason that the number of cases usually differs from the number of complaints is because some complaints involve more than one respondent company and because some complaints do not become cases at all, usually because no *prima facie* case is established.

Of the 366 rulings made by the Code of Practice Panel in 2003, 301 (82%) were accepted by the parties, 45 (12.5%) were unsuccessfully appealed and 20 (5.5%) were successfully appealed. This compares with the 4% of rulings which were successfully appealed in 2002.

The Code of Practice Panel met 88 times in 2003 (79 in 2002) and the Code of Practice Appeal Board met 13 times in 2003 (9 in 2002). The Appeal Board considered appeals in 29 cases as compared with 26 in 2002.

The number of complaints made by pharmaceutical companies in 2003 exceeded the number made by health professionals, there being 58 from pharmaceutical companies and 40 from health professionals. Historically the usual pattern was that the highest number of complaints each year came from health professionals but that has not been the case in four out of the last five years. Complaints made by pharmaceutical companies are usually more complex than those from outside the industry and generally raise a number of issues.

Advice on the application of the Code

Members of the Authority are always willing to advise on the application and interpretation of the Code and their direct line telephone numbers are included in the Code of Practice Review. They try to help enquirers and are usually able to do so.

They cannot, however, approve promotional material or activity and the decision as to whether or not to proceed is one for the company's signatories to take. If a complaint is subsequently received it will be dealt with in the usual way. It has to be borne in mind that the three members of the Authority, who also make up the Code of Practice Panel, do not have the last word on the application and interpretation of the Code as their rulings can be overturned by the Code of Practice Appeal Board.

If, as recently happened, a provider, or potential provider, of services to the industry implies that a novel form of promotion, or a novel way of approaching health professionals or hospitals, has the approval of the Authority, or of the ABPI itself, this is unlikely to be true and the Authority should be consulted before any reliance is placed upon what has been said.

Public reprimand for Schwarz Pharma

Schwarz Pharma Limited has been publicly reprimanded by the ABPI Board of Management for failing to provide within the requisite period of time the undertaking and assurance required in relation to a ruling that it had breached the Code of Practice.

The company withdrew the material at issue in good time as it had been superseded but was concerned that signing the undertaking would conflict with the product's marketing authorization and summary of product characteristics. The requisite undertaking and assurance has been given and full details can be found at page 3 in this issue of the Review in the report for Case AUTH/1405/1/03.

Dr Joy Edelman

The Authority received with sadness the news that Dr Joy Edelman had died on 10 July. Joy was an independent medical member of the Code of Practice Appeal Board from October 1999 until earlier this year. She made a valuable contribution to the work of the Appeal Board.

Honours for Appeal Board member

The Authority is pleased to record two awards to Mrs Linda Stone, a pharmacist member of the Code of Practice Appeal Board.

In May, Linda was awarded the Charter Gold Medal for 2004 of the Royal Pharmaceutical Society of Great Britain

Honours for Appeal Board member *continued*

in recognition of her contribution to the profession of pharmacy, and in the Queen's birthday honours she was appointed an officer of the Order of the British Empire for services to the National Health Service in the West Midlands.

Linda is a former Vice-President, President and Treasurer of the Royal Pharmaceutical Society, the only woman to have held all three offices

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.

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

Monday, 1 November

Friday, 3 December

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

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

How to contact the Authority

Our address is:

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12 Whitehall
London SW1A 2DY

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

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

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

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

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

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

CASE AUTH/1405/1/03

NORGINE v SCHWARZ PHARMA

Promotion of Idrolax

Norgine complained about the promotion of Idrolax (macrogol 4000 oral powder) by Schwarz Pharma. At issue were an eight page booklet entitled 'MIMS for Nurses' and a four page leavepiece. Norgine supplied Movicol as an oral powder containing macrogol 3350 plus electrolytes (macrogol oral powder compound).

Norgine stated that the booklet appeared to be the publication entitled 'MIMS for Nurses' dated August 2002. 'MIMS for Nurses' had not been formally launched. The booklet was a reprint of the nurse prescribing section of 'MIMS Companion' Spring 2002, produced specially for Schwarz, with the addition of Idrolax referred to as macrogol oral powder 4000. This was necessary because Idrolax had not been launched at the time 'MIMS Companion' Spring 2002 was published.

Norgine noted that the front cover of 'MIMS for Nurses' August 2002 had the appearance of a MIMS publication and it was only on closer examination that one could see that two out of the three boxes on the front page under the heading 'NURSE PRESCRIBING' contained promotional messages for Idrolax. Norgine alleged that this item constituted disguised promotion.

The Panel noted that 'MIMS Companion' was a twice yearly supplement to MIMS; the Spring 2002 copy was a special edition of that publication for nurses. A section on nurse prescribing, under therapy area headings, listed those items prescribable by nurses under the extended scheme. 'Macrogol oral powder, compound' (Movicol) was listed under the heading of constipation. In August 2002 Idrolax became available for nurse prescribing. Meanwhile the publishers of MIMS had decided that the next edition of 'MIMS Companion', due in November 2002, would be re-named 'MIMS for Nurses'. With the availability of Idrolax for nurses to prescribe, Schwarz decided to sponsor an updated version of the eight page nurse prescribing section which had originally appeared in 'MIMS Companion' Spring 2002. The only updating required was the addition of 'Macrogol oral powder 4000' (Idrolax) to the section on constipation. The updated booklet was issued in August 2002 under the title of 'MIMS for Nurses'. It was the first time that the publication 'MIMS for Nurses' appeared.

The front cover of the sponsored booklet had the typical appearance of a MIMS publication in that there were a number of highlighted boxes of information. Three of these boxes contained information or claims for Idrolax. Towards the bottom of the front cover was a statement that the booklet had been supported by an educational grant from Schwarz Pharma Limited. The inside front cover and the back cover both featured advertisements for Idrolax. Nurses could request copies of the booklet from Schwarz representatives.

Copies of the booklet at issue had been distributed through Schwarz's field force. The booklet referred to macrogol oral powder 4000 and the front cover included claims for Idrolax. Two advertisements for Idrolax had been included. The Panel considered that Schwarz was thus liable under the Code for the booklet. In the Panel's view most readers would assume that the booklet was an official edition of 'MIMS for Nurses' which was not so. The declaration of sponsorship did not negate this impression. The booklet, which included claims for Idrolax, had been specially produced for Schwarz. The Panel considered that the booklet constituted promotional material for Idrolax disguised as a copy of 'MIMS for Nurses'. A breach of the Code was ruled.

Norgine alleged that the entry for macrogol oral powder 4000 was misleading. 'MIMS Companion' Spring 2002, upon which the entries were based, had an entry for 'macrogol oral powder, compound' (Movicol). The reprinted version used for this promotional material was identical with the exception of a change to the entry for Norgine's product and an additional entry for Idrolax. The effect of this was that the modified entry relegated Norgine's product to secondary prominence to the Schwarz product, and did not clearly differentiate between them. This manipulation of the text was misleading. When 'MIMS for Nurses' was launched there would be separate entries for macrogol oral powder and macrogol oral powder, compound, which was appropriate as they were different products with different indications.

The Panel noted that in 'MIMS Companion' Spring 2002 the nurse prescribing section listed, under therapy area headings, those items prescribable by nurses under the extended scheme. Within each therapy area the generic names of the medicines prescribable were listed in alphabetical order. Where a generic product was available to be given by the same route but in a number of different forms, all of those forms were listed together. The entry for macrogol read 'Macrogol oral powder, compound' as at the time the only product available was Norgine's Movicol.

With the sponsorship of 'MIMS for Nurses' August 2002 the nurse prescribing list was updated as Idrolax had been launched and was now available for nurses to prescribe. The entry for macrogol now read 'Macrogol oral powder 4000, oral powder compound'. Thus, in effect, Idrolax was listed before Movicol. The Panel did not consider that the way in which the macrogol entry had been updated was unreasonable. The Panel did not consider that the information was incomplete, inaccurate or misleading. No breach of the Code was ruled.

Norgine noted that the claim in the leavepiece 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was referenced to Hudziak *et al* (1996).

This paper was originally published in French, with an abstract in English. The English abstract stated: 'With 20g of PEG 4000, electrolytes [sic] addition is

not necessary'. However, at the end of the discussion section of the original paper the authors stated that in the short-term, prescribing a low dose of PEG did not necessitate the addition of electrolytes. Norgine stated that the omission of the phrase 'short-term' in the claim substantially altered the meaning. Norgine would have no problem with the claim if it accurately reflected the meaning of the authors by stating, for example 'Idrolax had no added electrolytes because there is no significant electrolyte loss in short-term use'. Norgine alleged that the claim was misleading, incapable of substantiation and did not accurately reflect the meaning of the authors of the paper on which it was based.

The claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was referenced to Hudziak *et al*; it was not, however, presented as a quotation from that paper. There could therefore be no breach of the Code in that regard and the Panel ruled accordingly.

Hudziak *et al* was a short-term randomized, placebo-controlled, cross-over study. Healthy volunteers (n=16) were given either 20g macrogol 4000 per day or placebo during two seven day treatment periods. Blood electrolytes were measured; no significant variations with either active or placebo were observed. Denis and Lerebours (1997) was a long-term tolerability study in patients (n=16) suffering from functional constipation. The majority of patients took 10-20g/day macrogol 4000 for a mean period of 17.3 months. Blood electrolytes were assessed but no anomalies were detected under treatment. Couturier and Licht (1996) was a single-blind, randomized, multi-centre comparative study of macrogol 4000 versus lactulose on patients with functional constipation (n=232) treated for one month. Patients in the macrogol 4000 group (n=118) took 10-20g/day. Blood electrolytes were measured on day 0 and day 28; no significant changes during treatment were detected. Denis *et al* (1997) also compared the tolerability of macrogol 4000 and lactulose for the treatment of functional constipation in a 3 month study. Blood electrolytes were assessed but no anomalies were observed.

The Panel considered that the claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was supported by the data. Hudziak *et al* was relevant to the claim and had been cited in support of it although there were other papers which further supported the claim. On the basis of all of the data provided the Panel considered that the claim was not misleading and that it could be substantiated. No breach of the Code was ruled.

Upon appeal of this ruling by Norgine, the Code of Practice Appeal Board considered that the claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was a broad unequivocal claim. Although the claim made no reference to duration of therapy the Appeal Board noted the second bullet point on page 2 of the leavepiece stated 'Just as well tolerated [as lactulose] even with long term use'. The leavepiece thus referred to the long-term use of Idrolax and so the unqualified claim in question would have to be substantiable in those circumstances.

The Appeal Board noted that many patients required long-term use of laxative therapy; it was not unusual for such patients to be treated for many months. The Appeal Board noted the submission that the claim at issue was substantiated in the long term by data from a study on only 16 patients which had lasted for 17 months (Denis and Lerebours). The other studies cited by Schwarz either involved healthy volunteers (Hudziak) or were conducted for 3 months or less (Denis *et al*, Couturier and Licht). Further, only one study (Hudziak) measured faecal electrolytes which the Appeal Board considered was the most relevant measurement. Within the context of treating patients for chronic symptomatic constipation the Appeal Board considered that the 17 month data was insufficient. The Appeal Board thus considered that the claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was not substantiated by the data and was hence misleading. The Appeal Board ruled breaches of the Code.

Schwarz failed to provide the requisite undertaking and assurance in acceptance of this ruling within the time allowed by the Authority's Constitution and Procedure. This was reported by the Authority to the Appeal Board and the Appeal Board reported the matter to the ABPI Board of Management.

Schwarz stated that its view was that the ruling was not a fair interpretation of the scientific data or the marketing authorization and subsequent/ongoing seven years' post-marketing surveillance. On signing the undertaking the company would be limited to making claims that referred to no/insignificant electrolyte loss only in the short term which it considered was not a fair reflection of the summary of product characteristics (SPC) which, Schwarz submitted, did not restrict the use of Idrolax to short term administration. Schwarz considered that plasma electrolytes were the most relevant measurement.

The ABPI Board noted that its role was not to consider the merits of the ruling but to decide whether further sanctions should be applied.

Schwarz subsequently provided the requisite undertaking and assurance whilst still maintaining the points which it had made. The material at issue was last used in March 2003.

As the undertaking and assurance had not been given within the period allowed by the Constitution and Procedure, the ABPI Board publicly reprimanded Schwarz.

Norgine Limited complained about the promotion of Idrolax (macrogol 4000 oral powder) by Schwarz Pharma Limited. The items at issue were an eight page booklet entitled 'MIMS for Nurses' and dated August 2002, and a four page leavepiece (ref IDR2132A/MAR02). Norgine supplied Movicol as an oral powder containing macrogol 3350 plus electrolytes (macrogol oral powder compound). Norgine stated that it had not been possible to resolve its concerns directly with Schwarz.

A 'MIMS for Nurses' August 2002

1 Alleged disguised promotion

COMPLAINT

Norgine stated that this item appeared to be the publication entitled 'MIMS for Nurses', dated August 2002. 'MIMS for Nurses' had not been formally launched. The booklet was a reprint of the nurse prescribing section of 'MIMS Companion' Spring 2002, produced specially for Schwarz, with the addition of Idrolax referred to as macrogol oral powder 4000. This was necessary because Idrolax had not been launched at the time 'MIMS Companion' Spring 2002 was published.

Norgine noted that the front cover of 'MIMS for Nurses' August 2002 had the appearance of a MIMS publication and it was only on closer examination that one could see that two out of the three boxes under the heading 'NURSE PRESCRIBING' contained promotional messages for Idrolax. Norgine alleged that this item constituted disguised promotion in breach of Clause 10.1 of the Code.

RESPONSE

Schwarz stated that Idrolax was included in the Nurse Prescribers Formulary from August 2002, as listed in the Drug Tariff. In order to inform nurses who did not receive copies of the Drug Tariff of this change, Schwarz decided to sponsor a reprint of the MIMS publication on nurse prescribing. MIMS initiated the planned name change for the reprint, bringing it forward from November 2002 to August 2002, the date of publication. At the same time, MIMS ensured the publication was up-to-date. Schwarz noted that prescribing nurses had had a number of their prescriptions declined by pharmacists through lack of awareness of products being on the Nurse Prescribers Formulary. 'MIMS for Nurses' August 2002 provided an up-to-date resource of available medicines which could be prescribed by nurses; copies were available for nurses to request from members of the Schwarz field force.

Schwarz had no editorial input into the content of the item, nor into the editorial process that generated the statements of fact regarding Idrolax on the front cover. This was confirmed by the publishers in a letter supplied by Schwarz.

The content within the booklet was in the format used for the nurse prescribing section of 'MIMS Companion' Spring 2002 rather than being a 'reprint' as alleged by Norgine. The section had been updated by MIMS to reflect all changes to the Nurse Prescribing Formulary section of the Drug Tariff. However, there was only one change – the addition of macrogol oral powder 4000. Again, Schwarz had no input into the format used by MIMS. Macrogol oral powder 4000 was added in alphabetical order, the publishers of MIMS deciding this preceded macrogol oral powder compound in its format.

The front cover clearly stated that the publication was 'Supported by an educational grant from Schwarz Pharma Limited' as required by Clause 9.9 of the Code. This was followed by the statement 'This is a specialised reprint produced by [the publishers of MIMS]' and copyrighted to the publishers of MIMS. These statements clearly highlighted the fact that this publication was not disguised promotion and the editorial content was independently produced by the publishers of MIMS.

As such, Schwarz refuted the allegation that the item constituted disguised promotion in breach of Clause 10.1 of the Code, given its compliance with Clauses 9.9 and 10.1. It was stated that the specialised reprint was sponsored by Schwarz and the format was similar to any MIMS publication which contained information on the front cover relating to product updates.

PANEL RULING

The Authority did not have access to 'MIMS Companion' Spring 2002 or 'MIMS for Nurses' November 2002 and so the publisher was asked to supply copies which it did. In addition the publisher supplied a copy of the booklet at issue, a specialist reprint dated November 2002 and a letter dated 10 January that it had sent to Schwarz (a copy of this letter had been supplied in Schwarz's response).

The Panel noted that 'MIMS Companion' was a twice yearly supplement to MIMS; the Spring 2002 copy was a special edition of that publication for nurses. On pages 287-294 was a section on nurse prescribing which, under therapy area headings, listed those items prescribable by nurses under the extended scheme. 'Macrogol oral powder, compound' (Movicol) was listed under the heading of constipation. In August 2002 Idrolax became available for nurse prescribing. Meanwhile the publishers of MIMS had decided that the next edition of 'MIMS Companion', due in November 2002, would be re-named 'MIMS for Nurses'. However, with the availability of Idrolax for nurses to prescribe, Schwarz decided to sponsor an updated version of the eight page nurse prescribing section which had originally appeared in 'MIMS Companion' Spring 2002. The only updating which was required was the addition of 'Macrogol oral powder 4000' (Idrolax) to the section on constipation. The section was duly updated by the publishers and the eight page booklet was issued in August 2002 under the title of 'MIMS for Nurses'. It was the first time that the publication 'MIMS for Nurses' would have appeared.

The front cover of the sponsored booklet had the typical appearance of a MIMS publication in that there were a number of highlighted boxes of information. Three of these boxes contained information or claims for Idrolax. Towards the bottom of the front cover was a statement that the booklet had been supported by an educational grant from Schwarz Pharma Limited. The inside front cover and the back cover both featured advertisements for Idrolax. Nurses could request copies of the booklet from Schwarz representatives.

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided that the content of such material would be subject to

the Code if it was promotional in nature or if the company had used it 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 Panel noted that copies of the booklet at issue had been distributed through Schwarz's field force. The booklet referred to macrogol oral powder 4000 and the front cover included claims for Idrolax. Two advertisements for Idrolax had been included. The Panel considered that Schwarz was thus liable under the Code for the booklet. In the Panel's view most readers would assume that the booklet was an official edition of 'MIMS for Nurses' which was not so. The declaration of sponsorship did not negate this impression. The booklet, which included claims for Idrolax, had been specially produced for Schwarz. The Panel considered that the booklet constituted promotional material for Idrolax disguised as a copy of 'MIMS for Nurses'. A breach of Clause 10.1 was ruled. This ruling was not appealed.

2 Alleged incomplete and inaccurate information

COMPLAINT

Norgine alleged that the entry for macrogol oral powder 4000 was misleading. 'MIMS Companion' Spring 2002, upon which the entries were based, had an entry for 'macrogol oral powder, compound' (Movicol). The reprinted version used for this promotional material was identical with the exception of a change to the entry for Norgine's product and an additional entry for Idrolax. The effect of this was that the modified entry relegated Norgine's product to secondary prominence to the Schwarz product, and did not clearly differentiate between them. This manipulation of the text was misleading and appeared to have been done in order to give a greater prominence to the Schwarz product compared to Norgine's. When 'MIMS for Nurses' was launched there would be separate entries for macrogol oral powder and macrogol oral powder, compound, which was quite appropriate as they were different products with different indications.

Norgine alleged that the manipulation of the original text from 'MIMS Companion' Spring 2002, to produce the text contained in 'MIMS for Nurses' August 2002, resulted in incomplete and inaccurate information which was therefore misleading in breach of Clause 7.2.

RESPONSE

Schwarz stated that it had had no input into the editorial processes, content and presentation format of 'MIMS for Nurses' August 2002. The format was similar to that used for the nurse prescribing section of the 'MIMS Companion' Spring 2002, with alphabetical listings. Any decisions and control for using a similar format for 'MIMS for Nurses' August 2002 were entirely the responsibility of the editors of MIMS.

The entry for macrogols which appeared in 'MIMS for Nurses' August 2002 had been updated from that contained in the nurse prescribing section of 'MIMS Companion' Spring 2002 to reflect the inclusion of macrogol oral powder 4000 in the nurse prescribers' formulary. No manipulation of the text (which Norgine appeared to imply was deliberate) was instigated by Schwarz to produce misleading information and provide greater prominence to its product.

The presentation format utilised by the publisher for the macrogol entry followed the same format as other active ingredients. The active ingredient was stated initially with alternative presentations or formulations listed subsequently and separated by commas without repeating the major active ingredient. All such formulations were under the general heading of constipation, and drew no distinction in terms of specific indications within this general therapeutic area.

'MIMS for Nurses' August 2002 was a specialised reprint produced by the publishers of MIMS and followed a similar format to the nurse prescribing section of 'MIMS Companion' Spring 2002. Schwarz stated that it was misleading of Norgine to state that when 'MIMS for Nurses' was launched there would be separate entries for macrogol oral powder and macrogol oral powder, compound as the publishers allowed no influence over their standard format in their 'specialised reprint', 'MIMS for Nurses' August 2002. The format for 'MIMS for Nurses' August 2002 was determined by the publisher at the time of publishing, and it would have been its right to adapt the format for subsequent versions of 'MIMS for Nurses'. The publishers had confirmed that the format was its standard format, not open to external influence. Subsequently, in 'MIMS for Nurses' November 2002 the publishers expanded all entries to a format reflecting the monthly version of MIMS. This provided separate entries for such products as macrogol oral powder and macrogol oral powder, compound.

Schwarz refuted the allegation that there was deliberate manipulation of the original text from 'MIMS Companion' Spring 2002 giving inaccurate information that was misleading in breach of Clause 7.2. The reprint included a statement regarding sponsorship, the format was not influenced by Schwarz, the entry was in alphabetical order and the internal format was similar to that of the 'MIMS Companion' and information on the front cover relating to product updates was similar to that of MIMS publications.

PANEL RULING

The Panel noted that in 'MIMS Companion' Spring 2002 the nurse prescribing section listed, under therapy area headings, those items prescribable by nurses under the extended scheme. Within each therapy area the generic names of the medicines

prescribable were listed in alphabetical order. Where a generic product was available to be given by the same route but in a number of different forms, all of those forms were listed together. For example the entry for oral docusate in the constipation section read 'Docusate capsules, oral solution, oral solution paediatric'. The entry for macrogol read 'Macrogol oral powder, compound' as at the time the only product available was Norgine's ie Movicol.

With the sponsorship of 'MIMS for Nurses' August 2002 the nurse prescribing list was updated as Idrolax had been launched and was now available for nurses to prescribe. The entry for macrogol now read 'Macrogol oral powder 4000, oral powder compound'. Thus, in effect, Idrolax was listed before Movicol. The Panel did not consider that the way in which the macrogol entry had been updated was unreasonable. The Panel did not consider that the information was incomplete, inaccurate or misleading. Although the nurse prescribing list had been updated by the publishers of MIMS, the Panel noted from its comments in point 1 above that Schwarz was nonetheless liable under the Code for the content of 'MIMS for Nurses' August 2002. No breach of Clause 7.2 was ruled. This ruling was not appealed.

B Leavepiece

Claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss'

This claim appeared as the last of six bullet points on the back page of the leavepiece.

COMPLAINT

Norgine noted that the claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was referenced to Hudziak *et al* (1996).

This paper was originally published in French, with an abstract in English. The English abstract stated: 'With 20g of PEG 4000, electrolytes [sic] addition is not necessary'. However, at the end of the discussion section of the original French paper the authors stated 'In the short-term, prescribing a low dose of PEG does not necessitate the addition of electrolytes'. Norgine stated that the omission of the phrase 'short-term' in the claim substantially altered the meaning of the authors' findings. Norgine would have no problem with the claim if it accurately reflected the meaning of the authors by stating, for example, 'Idrolax had no added electrolytes because there is no significant electrolyte loss in short-term use'.

Norgine alleged that the claim was misleading, incapable of substantiation and did not accurately reflect the meaning of the authors of the paper on which it was based in breach of Clauses 7.2, 7.4 and 11.2.

RESPONSE

Schwarz stated that the leavepiece at issue was distributed by members of its field force. It was included as part of a single mailing in April 2002 (IDR2202/APR02).

The claim at issue was referenced to Hudziak *et al* in which macrogol oral powder 4000 was studied over a period of 14 days in 16 subjects. The authors concluded 'In the short-term, prescribing a low dose of [macrogol] does not necessitate the addition of electrolytes'. However, the claim at issue was not limited to short-term use. Use in the longer term with no significant electrolyte loss was substantiated by a number of additional clinical papers. Qualifying the claim with the addition of 'in short-term use' or similar such statements was not consistent with the available evidence in the use of macrogol oral powder 4000.

Schwarz referred to four studies and noted the following:

Hudziak *et al* studied macrogol powder 4000 over a period of 7 days for active treatment in 16 subjects. During the short-term treatment, no significant variation was observed in blood parameters for either active treatment or placebo. Denis and Lerebours (1997) studied macrogol 4000 in 16 patients for an average of more than 17 months. Treatment was not associated with any anomalies of blood electrolytes. Couturier and Licht (1996) compared macrogol 4000 (118 patients) with lactulose (114 patients) during 28 days of treatment. No significant variation from physiological ranges of electrolytes was observed. Denis *et al* (1997) compared macrogol 4000 (113 patients) with latulose (62 patients) during the three months' treatment. There was no significant difference in blood electrolytes between treatment groups or in individuals at the beginning and end of the study period.

The use of references to substantiate claims was only a requirement under the Code when direct reference was made to a published study (Clause 7.6). The claim in question did not make such reference, and would, therefore, not require use of any references to be stated on the leavepiece. However, the use of Hudziak *et al* was included as an illustrative reference.

Idrolax was granted UK marketing authorization in January 2002. The regulatory authority would have considered the labelling in the context of similar products. There was no requirement for limiting the use of Idrolax to the short-term, and the potential for electrolyte loss would have been part of the consideration. Thus, the claim remained in line with the marketing authorization, which did not restrict Idrolax use to the short-term in the treatment of adults with symptomatic constipation.

Schwarz submitted that the claim at issue was not misleading and that it was based on an up-to-date evaluation of all the evidence and that it reflected that evidence clearly. The claim could be substantiated. The company denied breaches of Clauses 7.2 and 7.4.

It was alleged that the claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' did not accurately reflect the meaning of the authors of the paper on which the claim was based and was in breach of Clause 11.2 which stated 'quotations from medical and scientific literature or from personal communications must accurately reflect the meaning of the author'. The claim at issue was not a quotation from the referenced clinical study.

The claim was based on substantiating evidence derived from a number of clinical studies, but provided with an illustrative reference. Schwarz refuted the allegation that the claim was in breach of Clause 11.2 given that it was not a quotation and that it reflected the currently available evidence from a number of sources.

PANEL RULING

The claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was referenced to Hudziak *et al*; it was not, however, presented as a quotation from that paper. There could, therefore be no breach of Clause 11.2 of the Code and so the Panel ruled accordingly.

The Panel noted that Hudziak *et al* was a short-term randomized, placebo-controlled, cross-over study. Healthy volunteers (n=16) were given either 20g macrogol 4000 per day or placebo during two seven day treatment periods. Blood electrolytes were measured at each step in the study; no significant variations with either active or placebo were observed. Denis and Lerebours was a long-term tolerability study in patients (n=16) suffering from functional constipation. The majority of patients took 10-20g/day macrogol 4000 for a mean period of 17.3 months. Blood electrolytes (Na+, Cl–, K+ and bicarbonates) were assessed but no anomalies were detected under treatment. Couturier and Licht was a single-blind, randomized, multi-centre comparative study of macrogol 4000 versus lactulose. Patients with functional constipation (n=232) were randomised into two treatment groups and treated for one month. Patients in the macrogol 4000 group (n=118) took 10-20g/day. Blood electrolytes were measured on day 0 and day 28; no significant changes during treatment were detected. Denis *et al* also compared the tolerability of macrogol 4000 and lactulose for the treatment of functional constipation in a 3 month study. Blood electrolytes were assessed but no anomalies were observed.

The Panel considered that the claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was supported by the data. Hudziak *et al* was relevant to the claim and had been cited in support of it although there were other papers which further supported the claim. On the basis of all of the data provided the Panel considered that the claim was not misleading and that it could be substantiated. No breach of Clauses 7.2 and 7.4 was ruled. This ruling was appealed.

APPEAL BY NORGINE

Norgine noted that Schwarz, in its assertion that the claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was substantiable and therefore not in breach of Clause 7.4, had cited Hudziak *et al*, Denis and Lerebours, Couturier and Licht and Denis *et al*. Norgine did not accept that these studies supported the extremely broad claim that 'there is no significant electrolyte loss'. Norgine considered that there were circumstances with the use of macrogol laxative agents, particularly if used in higher doses, when electrolyte loss could occur.

Norgine stated that as Hudziak *et al* was conducted in 16 healthy male volunteers over 7 days the only conclusion that could have been reached from the design of the study was that over 7 days no electrolyte loss was seen. Norgine noted that the authors therefore reasonably concluded that the study showed that in the conditions of short-term prescribing of a low dose of PEG (macrogol), electrolyte loss did not occur and that in these conditions (short-term use in healthy volunteers) the addition of electrolytes was not necessary.

Norgine considered that the justification Schwarz made for using Hudziak *et al* was not credible. Schwarz seemed to be stating that as no direct reference was made to a published study with respect to this claim it did not need to quote any specific reference at all, but nevertheless decided to quote Hudziak *et al* as an 'illustrative reference'. This begged the question that if Schwarz was going to use an 'illustrative reference' why use a reference that did not illustrate the claim it was making?

Norgine alleged that readers would gain the misleading impression that Hudziak *et al* substantiated the claim of 'no significant electrolyte loss' in all circumstances (low and high dose, short-term and long-term use) and in all patient groups, which it did not. As Schwarz had argued that the claim was substantiated by the other studies quoted, Norgine asked why it did not reference one or more of these other studies rather than the one that did not support the broad claim.

COMMENTS FROM SCHWARZ

Schwarz stated that it was unfortunate that Norgine did not accept that the four studies supported the claim 'no significant electrolyte loss'. Clearly, the studies did support the claim under normal prescribing circumstances. Schwarz noted that Norgine considered that there were circumstances with the use of macrogol laxative agents, particularly if used in higher doses, when electrolyte loss could occur. However Idrolax was promoted in accordance with the marketing authorization ie one to two sachets daily for the treatment of symptomatic constipation. This was in contrast to the higher doses that might be used in cases of faecal impaction for which Norgine's product Movicol, was licensed; Schwarz expected Norgine to appreciate the licensed differences between the two products. The claim stated 'no significant electrolyte loss', which remained within the context of the treatment of symptomatic constipation, had allowed for the fact that there might be individual variations within a normal range seen in clinical practice and was substantiated by the four clinical studies cited.

In addressing the Panel's ruling of no breach of Clause 7.2 Schwarz maintained that the claim reflected currently available evidence, as substantiated by the four clinical studies. The use of references to substantiate claims was only a requirement under the Code when direct reference was made to a published study. Schwarz submitted that the claim at issue was substantiated by all four studies, of which Hudziak *et al* was used as an illustrative example. Schwarz re-

iterated that Norgine's suggestion that the claim must be substantiated 'in all circumstances (low and high dose, short-term and long-term use) and in all patient groups' was not acceptable. Schwarz submitted that Norgine's suggestion implied that it was acceptable to promote outside the terms of a marketing authorization.

Schwarz stated that the decision to select the references used to support claims was an internal process that was continually reviewed. Schwarz submitted that with regard to the appeal against the ruling of no breach of Clause 7.2 the issue of reference selection in promotional material was not relevant, there was no indication in the promotional material that Hudziak *et al* alone substantiated the claim. Schwarz noted that no treatment duration was quoted, and there were studies to substantiate the claim in short-term and long-term use according to the licensed posology of Idrolax. There was no requirement to reference all evidence sources in promotional material and Schwarz had fulfilled the requirements of Clauses 7.2 and 7.4 by providing an up-to-date evaluation of the evidence. Schwarz submitted that it had repeatedly demonstrated that the claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was substantiated for licensed doses of Idrolax in the short-term and long-term (up to 17 months studied) treatment of symptomatic constipation.

Schwarz noted that in appealing the Panel's ruling of no breach of Clause 7.4 Norgine had asserted that the four clinical studies cited did not substantiate the claim. Norgine had not offered any scientific counter to the clinical supporting studies; in its appeal the company's focus was entirely on Hudziak *et al* without consideration of the three additional studies provided to substantiate the claim. Schwarz submitted that the subsequent content of the appeal criticised the Hudziak paper. Schwarz submitted that it was misleading of Norgine to suggest that a single study could substantiate such a claim when it quoted situations where it was not appropriate to prescribe Idrolax, ie high dose.

Schwarz stated that it found it difficult to respond to an appeal of the ruling of no breach of Clause 7.4 since Norgine presented no scientific argument as to how the four cited clinical studies did not substantiate the claim. Schwarz submitted that should it possess some indication as to Norgine's specific issues in this regard, its response might well be more appropriately directed.

FURTHER COMMENTS FROM NORGINE

Norgine made no further comments.

APPEAL BOARD RULING

Neither party chose to be represented when the matter was considered by the Appeal Board.

The Appeal Board considered that the claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was a broad unequivocal claim. Although the claim made no reference to duration of therapy the Appeal Board noted the second bullet point on page 2 of the leavepiece stated 'Just as well tolerated [as lactulose] even with long term use'. The leavepiece thus referred to the long-term use of Idrolax and so the unqualified claim in question would have to be substantiable in those circumstances.

The Appeal Board noted that many patients required long-term use of laxative therapy; it was not unusual for such patients to be treated for many months. The Appeal Board noted the submission that the claim at issue was substantiated in the long term by data from a study on only 16 patients which had lasted for 17 months (Denis and Lerebours). The other studies cited by Schwarz either involved healthy volunteers (Hudziak *et al*) or were conducted for 3 months or less (Denis *et al*, Couturier and Licht). Further, only one study (Hudziak *et al*) measured faecal electrolytes which the Appeal Board considered was the most relevant measurement. Within the context of treating patients for chronic symptomatic constipation the Appeal Board considered that the 17 month data was insufficient. The Appeal Board thus considered that the claim 'Idrolax has no added electrolytes because there is no significant electrolyte loss' was not substantiated by the data and was hence misleading. The Appeal Board ruled breaches of Clauses 7.2 and 7.4. The appeal was successful.

REPORT TO APPEAL BOARD

Schwarz declined to provide the requisite undertaking and assurance in acceptance of the Appeal Board's ruling that it was in breach of Clauses 7.2 and 7.4 of the Code. Although the item at issue had been superseded, Schwarz considered that signing the undertaking would potentially leave future materials that referred to electrolytes in breach of such an undertaking since the claim in question was consistent with the marketing authorization.

The Authority reported the failure to provide an undertaking and assurance to the Appeal Board in accordance with Paragraph 11 of the Authority's Constitution and Procedure.

When the report was considered by the Appeal Board, Schwarz stated its view that the ruling was not a fair interpretation of the scientific data or the marketing authorization and subsequent/ongoing seven years' post-marketing surveillance. On signing the undertaking the company would be limited to making claims that referred to no/insignificant electrolyte loss only in short-term use, which it considered was not a fair reflection of the product's summary of product characteristics (SPC) which, Schwarz submitted, did not restrict the use of Idrolax to short- term administration. Schwarz considered that plasma electrolytes were the most relevant measurement.

The Appeal Board decided to report Schwarz to the ABPI Board of Management in accordance with Paragraph 12.1 of the Constitution and Procedure.

REPORT TO ABPI BOARD OF MANAGEMENT

The ABPI Board noted that its role was not to review the merits of the rulings made by the Appeal Board but to consider whether further sanctions should be imposed.

Schwarz stated that in its view the Appeal Board ruling was in conflict with the marketing authorization for Idrolax. It believed that the Appeal Board ruling would require in future promotion an additional stipulation stating that electrolyte loss occurred in long-term use and this was unsubstantiable. Schwarz stated that it supported the Code but signing the undertaking would conflict with the marketing authorization and would result in future use of the statement leading to a breach of undertaking.

The ABPI Board was concerned Schwarz believed that the undertaking requested would conflict with the marketing authorization and the SPC. It was decided to ask the Chairman of the Appeal Board to comment on this point and the ABPI Board would then reconsider the matter.

FURTHER CONSIDERATION BY THE ABPI BOARD

The Board noted the Chairman's response to its request for informal assistance.

The ABPI Board asked the President to discuss the matter with the managing director of Schwarz. Following this discussion, Schwarz provided the requisite undertaking and assurance whilst still standing by the representations which it had made regarding the issue of electrolyte balance and macrogol 4000. Schwarz had not used the material in question since 24 March 2003. There had also been a change of managing director.

FURTHER CONSIDERATION BY THE ABPI BOARD

The ABPI Board noted that the undertaking and assurance had now been given by Schwarz and that the material had not been used since March 2003. Schwarz stood by the points made to the Appeal Board and the ABPI Board but it believed in self regulation and wanted to remain part of the system. Schwarz had left membership of the ABPI at the end of 2003.

The ABPI Board was concerned that Schwarz had not complied with the Authority's Constitution and Procedure as it had not provided the requisite undertaking and assurance by the due date of 9 July 2003. The ABPI Board therefore publicly reprimanded Schwarz.

Complaint received **2 January 2003**

Case completed **18 May 2004**

CASE AUTH/1544/1/04

JANSSEN-CILAG v NAPP

Promotion of OxyContin

Janssen-Cilag complained about the promotion of OxyContin (prolonged release oxycodone tablets) by Napp. OxyContin was indicated for the treatment of moderate to severe pain in patients with cancer and post-operative pain. In October 2003 the licence was extended to include the treatment of severe pain requiring the use of a strong opioid. The material at issue was a detail aid and a leavepiece. Janssen-Cilag supplied Durogesic (fentanyl).

Janssen-Cilag noted that oxycodone was also available in an immediate release formulation, OxyNorm. The distinction between OxyNorm and OxyContin had important patient safety related implications; the controlled release formulation should not be used in the immediate post-operative setting as it might cause respiratory embarrassment or exacerbate bowel related problems without the ability to be rapidly reversed.

Janssen-Cilag alleged that the unqualified claim '5mg starting dose in frail patients or those with renal or hepatic impairment' which appeared in both the detail aid and leavepiece on pages headed 'Straightforward dosing' and beneath two boxes of text which set out details of the starting dose and maintenance dose, was not in line with the OxyContin summary of product characteristics (SPC). OxyContin was contraindicated in patients with moderate to severe hepatic impairment or severe renal impairment.

The Panel noted the contraindication section of the OxyContin SPC stated: 'Respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, chronic obstructive airways disease, chronic bronchial asthma, hypercarbia, known oxycodone sensitivity, moderate to severe hepatic impairment, severe renal impairment (creatinine clearance <10ml/min), chronic constipation, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively. Pregnancy'.

The SPC gave details about dosing in various patient populations. The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids was 10mg, 12-hourly. In adult patients with mild to moderate renal impairment and mild hepatic impairment, dose initiation should follow a conservative approach. Opioid naïve patients should be started on OxyContin 5mg every 2 hours.

The Panel noted that OxyContin was contraindicated in patients with moderate to severe hepatic impairment and severe renal impairment. The claim at issue, however, gave the impression that patients with any degree of renal or hepatic impairment could have OxyContin treatment initiated at 5mg which was not so. The impression of a simple dosing choice was strengthened by the page heading 'Straightforward dosing'. The Panel considered that the claim was inconsistent with the SPC and thus ruled a breach of the Code. This ruling was not appealed.

Janssen-Cilag noted that the claim '75% of patients experienced pain relief by 15 minutes after a single 40mg dose' was referenced to Curtis *et al* (1999) and appeared on page 4 beneath a subheading 'Fast onset of action'. Page 4 was headed 'Easily titrated for rapid pain control'. This claim suggested that OxyContin 40mg was an acceptable starting dose for all indications (as the strapline which appeared at the bottom on the facing page stated 'For moderate to severe cancer or post-operative pain'), but this was not so. In addition, the claim implied that 40mg led to complete or satisfactory pain relief by 15 minutes for all indications, and was a starting dose for all patients, including opioid naïve patients; this was another unqualified claim. Janssen-Cilag alleged that the claim was misleading in breach of the Code. Janssen-Cilag also alleged that high standards had not been maintained with regard to patient safety.

The Panel considered that the claim '75% of patients experienced pain relief by 15 minutes after a single 40mg dose' was misleading and ambiguous as the data related to <u>onset</u> (emphasis added) of pain relief as stated by Napp whereas the claim could be read to refer to <u>complete</u> pain relief. The Panel ruled a breach of the Code. This ruling was not appealed.

The Panel did not consider that page 4 of the detail aid implied that 40mg was a starting dose for all patients for all indications. The starting dose according to the SPC depended upon the severity of the pain and the patient's previous analgesic history. Patients transferring from morphine should have the daily dose based on the ratio of 10mg oral oxycodone being equivalent to 20mg oral morphine. The Panel did not consider that the reference to the 40mg dose would be read as the starting dose for the product for all indications. The Panel therefore ruled no breach of the Code. This ruling was appealed by Janssen-Cilag.

The Appeal Board noted that the claim '75% of patients experienced pain relief by 15 minutes after a single 40mg dose' was referenced to Curtis *et al*, a randomised, double-blind trial which assessed, *inter alia*, the relative analgesic potency of single doses (20mg and 40mg) of oral controlled release oxycodone using a post-operative pain model. Patients had not been titrated up to a 40mg dose but had just received a one off dose of oxycodone. The Appeal Board considered that the wording on page 4 of the detail aid did not make it sufficiently clear that 40mg was not an appropriate starting dose. High standards had not been maintained. The Appeal Board therefore ruled a breach of the Code.

Janssen-Cilag alleged that there were a number of safety related issues with the detail aid and leavepiece. It was not clearly stated that OxyContin should not be started until 24 hours post-operatively as included in the contraindications for this particular indication. It was not clear that patients with severe renal or moderate to severe hepatic impairment should not be given OxyContin. The

prominent recommendation of the 40mg dose as a starting dose for all patients irrespective of the indication neglected the recommended starting dose of 10mg every 12 hours as stated in the SPC. Janssen-Cilag alleged that the cumulative effect of these breaches might compromise the safety of patients and so brought the industry into disrepute in breach of Clause 2 of the Code.

The Panel noted that the alleged breach of Clause 2 of the Code related to three matters; firstly the failure to state that OxyContin should not be started until 24 hours post-operatively. On balance the Panel accepted Napp's submission that the GP detail aid was appropriate for those patients who would be treated by a GP; neither the detail aid nor the leavepiece referred to patients in the immediate post-operative period although both referred to post-operative pain. Secondly, the implication that 40mg was the starting dose. In this regard the Panel noted its ruling above of no breach of the Code in relation to that claim. Thirdly, the failure to make it clear that patients with severe renal or moderate to severe hepatic impairment should not be given OxyContin. The Panel noted its ruling above of a breach of the Code regarding the claim '5mg starting dose in frail patients or those with renal or hepatic impairment'. The Panel considered that the claim might encourage doctors to prescribe OxyContin for patients who should not be so treated and therefore compromise patient safety. The Panel considered that such advertising brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel thus ruled a breach of Clause 2 of the Code. This ruling was appealed by Napp.

The Panel did not consider that the other two matters raised by Janssen-Cilag ie the failure to state that OxyContin should not be started until 24 hours post-operatively or the implication that 40mg was the starting dose warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure. The Panel thus ruled no breach of Clause 2 in those regards. This ruling was appealed by Janssen-Cilag.

The Appeal Board noted that Janssen-Cilag had complained that the cumulative effect of a number of issues relating to patient safety had been worthy of a ruling of a breach of Clause 2 of the Code. These issues related to the fact that OxyContin was contraindicated within the first 24 hours post-operatively and in patients with severe renal or moderate to severe hepatic impairment. Janssen-Cilag had considered that these contraindications had not been made sufficiently clear in the material at issue. Janssen-Cilag had also alleged that the failure to clearly state that 40mg was not a recommended starting dose was also prejudicial to patient safety.

The Appeal Board noted that the Panel had separated Janssen-Cilag's reasons for the alleged breach of Clause 2 such that each party would have the opportunity to appeal. The Appeal Board did not consider itself bound by this separation of the issues.

The Appeal Board was particularly concerned that the claim '5mg starting dose in frail patients or those with renal or hepatic impairment' gave the impression that patients with any degree of renal or hepatic impairment could be treated with OxyContin which was not so. Patients with either severe renal or moderate to severe hepatic impairment should not be treated with OxyContin at all.

With regard to the issue of post-operative use of OxyContin the Appeal Board noted that such use was referred to a number of times without qualification. 'For moderate to severe cancer or post-operative pain' was a heading on the front cover of the detail aid and a strapline on pages 3 and 5. The Appeal Board was concerned that it had not been made clear that post-operative pain in the first 24 hours after an operation could not be treated with OxyContin.

The Appeal Board also noted its ruling above that the claim '75% of patients experienced pain relief by 15 minutes after a simple 40mg dose' did not make it sufficiently clear that 40mg was not an appropriate starting dose.

Overall the Appeal Board considered that the detail aid and the leavepiece might lead to prescribing in patients for whom the product was contraindicated which might compromise patient safety and such advertising brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board thus ruled a breach of Clause 2.

Janssen-Cilag noted that page 5 of the detail aid was headed 'Very well tolerated' and referred to adverse event data from 5 studies involving 2,199 patients using OxyContin tablets. A bar chart gave the percentage of complaints of constipation as 3.9%. A footnote to the constipation data stated 'Two thirds of patients suffering constipation received a laxative. Prophylactic laxatives should always be considered with strong opioid treatment'. The data was referenced to 'data on file'.

Janssen-Cilag noted that the data was from a post-marketing surveillance study wherein the majority of patients were not treated in accordance with the terms of the UK marketing authorization. The reported constipation rate did not reflect the data from trials in the current licensed indications for OxyContin. Janssen-Cilag alleged that the claim for a low rate of constipation and the claim 'Very well tolerated' were in breach of the Code.

The Panel noted that the page did not make a claim for a low rate of constipation. The figure of 3.9% was not inconsistent with the limited data in the SPC. Published clinical studies gave rates of 21% and 30% dropping to 10% after 12 weeks of treatment. The Panel was, however, concerned that the categorical figure of 3.9% did not reflect the balance of the evidence. The Panel thus ruled a breach of the Code. This ruling was not appealed.

The Panel did not consider that the heading to the page 'Very well tolerated' in association with the data for constipation was exaggerated as alleged. No breach of the Code was ruled. This ruling was appealed by Janssen-Cilag.

The Appeal Board was concerned that data from such a post-marketing surveillance study, which relied on spontaneous reporting of adverse events, had been used as the basis for a safety claim. The

Appeal Board considered that 'Very well tolerated' was a strong claim. The Appeal Board considered that given the constipation data the claim was exaggerated as alleged and a breach of the Code was ruled.

Janssen-Cilag Ltd complained about the promotion of OxyContin (prolonged release oxycodone hydrochloride tablets) by Napp Pharmaceuticals Limited. OxyContin was indicated for the treatment of moderate to severe pain in patients with cancer and post-operative pain. In October 2003 the licence was extended to include the treatment of severe pain requiring the use of a strong opioid.

Janssen-Cilag supplied Durogesic (fentanyl).

The material at issue was a detail aid (OX03019) and a leavepiece (UK/OX-03028a) which were used by representatives when calling on GPs from June to December 2003. The material was no longer in circulation.

Janssen-Cilag stated that oxycodone was also available in an immediate release formulation, OxyNorm. The distinction between OxyNorm and OxyContin had important patient safety related implications; the controlled release formulation should not be used in the immediate post-operative setting as it might cause respiratory embarrassment or exacerbate bowel related problems without the ability to be rapidly reversed.

Janssen-Cilag referred to the OxyContin summary of product characteristics (SPC) (from the eMC website 15 December) and appeared to quote from the contraindications section that OxyContin was not 'recommended for pre-operative use or for the first 24 hours post-operatively, paralytic ileus, moderate to severe hepatic impairment, severe renal impairment and chronic constipation'.

1 Claim '5mg starting dose in frail patients or those with renal or hepatic impairment'

This claim appeared in both the detail aid and leavepiece on pages headed 'Straightforward dosing' and beneath two boxes of text which set out details of the starting dose and maintenance dose.

COMPLAINT

Janssen-Cilag alleged that the unqualified claim '5mg starting dose in frail patients or those with renal or hepatic impairment' was not in line with the OxyContin SPC in breach of Clause 3.2 of the Code. OxyContin was contraindicated in patients with moderate to severe hepatic impairment or severe renal impairment (creatinine clearance <10ml/min).

Janssen-Cilag had previously advised Napp of its concerns about the need to qualify the important product related contraindications and to communicate this information to physicians in promotion. Reference was made to inter-company correspondence.

RESPONSE

Napp stated that the contraindications section of the OxyContin SPC and prescribing information included 'moderate to severe hepatic impairment and severe renal impairment'. However, this did not contraindicate OxyContin tablets from all patients suffering from such impairments. Section 4.2 of the OxyContin SPC stated that opioid naïve patients with mild to moderate renal impairment and mild hepatic impairment should be started on OxyContin 5mg 12-hourly or OxyNorm liquid 2.5mg 6 hourly.

In any event, Napp's sales representatives were fully trained in the indications, dosage and administration and contraindications of all of Napp's products, and were instructed to make these points clearly to prescribers.

Napp supplied two items which it stated demonstrated that the sales representatives were fully trained in the appropriate starting dosage of OxyContin tablets for these impaired patients. Firstly an OxyContin update sheet, which was sent to each member of the sales force in September 2003 for inclusion in their OxyContin training manuals to update them on the new 5mg strength of OxyContin tablets. The update sheet stated that the '5mg strength can be used as a starting dose in patients with mild to moderate renal impairment and mild hepatic impairment…'. Secondly a test taken by all sales representatives who promoted OxyContin tablets. Two questions addressed the contraindications for patients with moderate to severe hepatic impairment and severe renal impairment. These items were representative of the training provided to the sales force since launch of OxyContin tablets, and these messages were reinforced at regular intervals. Janssen-Cilag's concerns that patient safety was compromised were unfounded.

PANEL RULING

The Panel noted the contraindication section of the OxyContin SPC (May 2002 and printed from the eMC 15 December 2003) stated: 'Respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, chronic obstructive airways disease, chronic bronchial asthma, hypercarbia, known oxycodone sensitivity, moderate to severe hepatic impairment, severe renal impairment (creatinine clearance <10ml/min), chronic constipation, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively. Pregnancy'.

This was not as quoted by Janssen-Cilag in its complaint.

The SPC gave details about dosing in various patient populations. The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids was 10mg, 12-hourly. In adult patients with mild to moderate renal impairment and mild hepatic impairment dose initiation should follow a conservative approach. Opioid naïve patients should be started on OxyContin 5mg every 2 hours.

The Panel noted Napp's submission that sales representatives were fully trained and instructed to make these points clearly. However promotional

material had to comply with the Code in its own right and not rely on clarification/further information from sales representatives.

The Panel noted that OxyContin was contraindicated in patients with moderate to severe hepatic impairment and severe renal impairment. The claim at issue, however, gave the impression that patients with any degree of renal or hepatic impairment could have OxyContin treatment initiated at 5mg which was not so. The impression of a simple dosing choice was strengthened by the page heading 'Straightforward dosing'. The Panel considered that the claim was inconsistent with the SPC and it thus ruled a breach of Clause 3.2 of the Code.

2 Claim '75% of patients experienced pain relief by 15 minutes after a single 40mg dose'

The claim was referenced to Curtis *et al* (1999) and appeared on page 4 of the detail aid beneath a subheading 'Fast onset of action'. Page 4 was headed 'Easily titrated for rapid pain control'.

COMPLAINT

Janssen-Cilag was concerned that this suggested that OxyContin 40mg was an acceptable starting dose for all indications (as the strapline which appeared at the bottom on the facing page (page 5) stated 'For moderate to severe cancer or post-operative pain'), but this was not so.

In addition, the claim implied that 40mg led to complete or satisfactory pain relief by 15 minutes for all indications, and was a starting dose for all patients, including opioid naïve patients; this was another unqualified claim.

Janssen-Cilag alleged that high standards had not been maintained in regard to patient safety with the claim at issue in breach of Clause 9.1 of the Code.

The primary outcomes of Curtis *et al* compared the relative potencies of controlled-release oxycodone and controlled-release morphine, as measured by the peak pain relief and the total pain relief. The range of time to peak pain relief was between 1.49 to 2.36 hours for controlled-release oxycodone. Curtis *et al* stated that the 'derived onset of relief was related to dose, with 75% of the patients reporting onset by 15 min'. The onset of action might have been at 15 minutes, but this could not be extrapolated to conclude that complete or satisfactory pain relief was achieved in this very short time. Janssen-Cilag alleged that the claim was misleading in breach of Clause 7.2 of the Code.

RESPONSE

Napp stated that a cursory review of the detail aid revealed that page 4 did not recommend 40mg as a starting dose. The claim at issue appeared under the bold sub-heading 'Fast onset of action' and was an example of the fast onset of pain relief at a certain dosage level, not the starting dose. The detail aid did not suggest that this was complete pain relief and referred to the speed of onset of initial pain relief, as indicated by the bold heading above. This factual claim was substantiated by Curtis *et al*.

Janssen-Cilag's complaint also needed to be reviewed in the context of the whole detail aid. On page 6, under the heading of 'Straightforward dosing', the starting dose of 10-20mg appeared in unmistakably large black letters. The upper range of the starting dose of 20mg and the asterisked wording appearing immediately below was based on wording in the 'Posology and method of administration' section of the SPC: 'The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements'.

In short, there was simply no confusion whatsoever in the materials about the correct starting dose. Far from being 'neglected' as alleged by Janssen-Cilag, the starting dose of 10-20mg appeared in prominent black letters on page 6. The wording Janssen-Cilag complained about on page 4 dealt with onset of pain relief, which was a completely different claim and one that was substantiated by Curtis *et al*.

PANEL RULING

The Panel did not consider that page 4 of the detail aid implied that 40mg was a starting dose for all patients for all indications. The starting dose according to the SPC depended upon the severity of the pain and the patient's previous analgesic history. Patients transferring from morphine should have the daily dose based on the ratio of 10mg oral oxycodone being equivalent to 20mg oral morphine. The Panel did not consider that the reference to the 40mg dose would be read as the starting dose for the product for all indications. The Panel therefore ruled no breach of Clause 9.1 of the Code. This ruling was appealed by Janssen-Cilag.

The Panel considered that the claim '75% of patients experienced pain relief by 15 minutes after a single 40mg dose' was misleading and ambiguous as the data related to onset (emphasis added) of pain relief as stated by Napp whereas the claim could be read to refer to complete pain relief. The Panel ruled a breach of Clause 7.2 of the Code. This ruling was not appealed.

APPEAL BY JANSSEN-CILAG

Janssen-Cilag noted that the claim '75% of patients experienced pain relief by 15 minutes after a single 40mg dose' had no qualifying or explanatory statement. It was therefore not made clear that this dose was wholly inappropriate for 'opioid naïve patients', and that 'some patients might benefit from a starting dose of 5mg to minimise the incidence of side effects' as stated in section 4.2 of the OxyContin SPC. The claim on page 4 of the detail aid was found under the section which started on page 3. There was no reference to the usual starting dose on page 3 or 4 of the detail aid. A clinician could therefore conclude that 40mg was a very effective dose and suitable for all patients.

Janssen-Cilag stated that clinicians might interpret 40mg to be a safe starting dose for some patients without explicitly being made aware of the fact that 40mg was not a normal starting dose, as illustrated by the fact that 80mg of OxyContin could cause fatal

respiratory depression when administered to opioid naïve patients as stated in section 4.4 of the OxyContin SPC.

Janssen-Cilag therefore alleged that high standards had not been upheld regarding the safety of patients, particularly the frail and opioid naïve patients, by the manner in which 40mg was prominently displayed on page 4, without any qualifying statements. A breach of Clause 9.1 was alleged.

COMMENTS FROM NAPP

Napp noted that the detail aid featured descriptive tabs on the top of the right-hand pages, starting with 'Efficacy' on pages 2 and 3, 'Pain Control/Tolerability' on pages 4 and 5 and 'Dosing/OxyNorm' on pages 6 and 7. The later tabs were visible to the reader when looking at the earlier inside pages of the detail aid. Napp submitted that when a reader was on page 4, where the claim at issue appeared, it was clear that this page was all about the onset of action and rapid titration to pain control. The next tab 'Dosing/ OxyNorm' was visible in the top right corner, which flagged up that dosing was covered on another page (page 6).

Napp submitted that by turning the page (to page 6), the reader saw a large banner, 'Straightforward dosing', with the starting dose of 10–20mg 12 hourly appearing in very large, bold, black lettering within a box. The starting dose information was therefore extremely prominent, and no-one would mistake the 40mg dose as an appropriate starting dose. The starting dose of 5mg for frail patients was also clearly stated below the box on page 6.

Napp submitted that high standards had been maintained with very prominent starting dose information, and patient safety was not being compromised and therefore Clause 9.1 had not been breached.

FURTHER COMMENTS FROM JANSSEN-CILAG

There were no further comments from Janssen-Cilag.

APPEAL BOARD RULING

The Appeal Board noted that the claim '75% of patients experienced pain relief by 15 minutes after a single 40mg dose' was referenced to Curtis *et al*, a randomised, double-blind trial which assessed, *inter alia*, the relative analgesic potency of single doses (20mg and 40mg) of oral controlled release oxycodone using a post-operative pain model. Patients had not been titrated up to a 40mg dose but had just received a one off dose of oxycodone. The Appeal Board considered that the wording on page 4 of the detail aid did not make it sufficiently clear that 40mg was not an appropriate starting dose. High standards had not been maintained. The Appeal Board therefore ruled a breach of Clause 9.1 of the Code. The appeal on this point was successful.

3 Alleged breach of Clause 2

COMPLAINT

Janssen-Cilag alleged that there were a number of safety related issues with the detail aid and leavepiece. It was not clearly stated that OxyContin should not be started until 24 hours post-operatively as included in the contraindications for this particular indication. It was not clear that patients with severe renal or moderate to severe hepatic impairment should not be given OxyContin despite its efforts to resolve this on an inter-company basis. The prominent recommendation of 40mg as a starting dose for all patients irrespective of the indication neglected the recommended starting dose of 10mg every 12 hours as stated in the SPC.

Janssen-Cilag alleged that the cumulative effect of these breaches might compromise the safety of patients, and so brought the industry into disrepute in breach of Clause 2 of the Code.

RESPONSE

With regard to Janssen-Cilag's complaint that it was not clearly stated that OxyContin should not be started until 24 hours post-operatively as included in the contraindications for this particular indication, Napp stated that the materials at issue were aimed at a GP/primary care audience, not pain consultants and anaesthetists who treated patients post-operatively. Napp had created a completely separate detail aid (OX03021) regarding the post-operative use of OxyContin, a copy of which was provided. That detail aid made it very clear that OxyContin tablets were contraindicated for 24 hours post-operatively. Reference was made to the prominent wording on pages 2 and 9 of that detail aid.

In Napp's view, the GP detail aid was entirely appropriate for the types of patients a GP would treat, which did not include patients who were in the immediate post-operative period. While the detail aid referred to the full licensed indication of 'moderate to severe cancer or post-operative pain' in several places (as indeed it was required to do), it did not mention or promote post-operative use in any of the substantive text. The contraindication was, of course, mentioned in that section of the prescribing information.

Napp submitted when promoting OxyContin for post-operative use, the sales representatives only used the detail aid that had been specifically designed for that indication, which highlighted this important contraindication very prominently. Patient safety was therefore assured.

PANEL RULING

The Panel noted that the alleged breach of Clause 2 of the Code related to three matters; firstly the failure to state that OxyContin should not be started until 24 hours post-operatively. On balance the Panel accepted Napp's submission that the GP detail aid was appropriate for those patients who would be treated by a GP; neither the detail aid nor the leavepiece referred to patients in the immediate post-operative period although both referred to post-operative pain. Secondly, the implication that 40mg

was the starting dose. In this regard the Panel noted its ruling in point 2 above of no breach of the Code. Thirdly, the failure to make it clear that patients with severe renal or moderate to severe hepatic impairment should not be given OxyContin. The Panel noted its ruling in point 1 above of a breach of the Code regarding the claim '5mg starting dose in frail patients or those with renal or hepatic impairment'. The Panel considered that the claim might encourage doctors to prescribe OxyContin for patients who should not be so treated and therefore compromise patient safety. The Panel considered that such advertising brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel thus ruled a breach of Clause 2 of the Code. This ruling was appealed by Napp.

The Panel did not consider that the other two matters raised by Janssen-Cilag ie the failure to state that OxyContin should not be started until 24 hours post-operatively or the implication that 40mg was the starting dose warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure. The Panel thus ruled no breach of Clause 2 in that regard. This ruling was appealed by Janssen-Cilag.

APPEAL BY NAPP

Napp submitted that it had not intended to compromise patients' safety in any way by stating '5mg starting dose in frail patients or those with renal or hepatic impairment'. On the contrary, the purpose of this claim was to warn doctors of the advice in the SPC that for certain classes of patient they should adopt a conservative approach and should not use a 10mg starting dose. The relevant part of section 4.2 of the SPC stated:

'The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10mg, 12-hourly. Some patients may benefit from a starting dose of 5mg to minimise the incidence of side effects.'

'Adults with mild to moderate renal impairment and mild hepatic impairment:The plasma concentration in this population may be increased. Therefore, dose initiation should follow a conservative approach. Opioid naïve patients should be started on OxyContin 5mg 12-hourly.'

Napp submitted that whilst it had accepted that the wording in its materials was not as precise as it should have been, there was no intention to suggest that the product could be used in patients for whom it was contraindicated. Napp submitted that it was focussed on ensuring that doctors were made aware of the correct doses for vulnerable categories of patients for whom the product was indicated, to avoid any risk to those patients.

Napp noted that there was a general presumption in the Code that doctors did not need to be made expressly aware of all contraindications for a product; the company could not think of an example of any promotional item for any product in which all the contraindications were highlighted. In the case of a patient with moderate to severe hepatic impairment or severe renal impairment it was reasonable to expect that the doctor would carefully check the contraindications of all medicines prescribed for that patient. So even if a doctor had focussed on the phrase in question it was unlikely that he or she would have been misled in practice to wrongly prescribe.

Napp submitted that in assessing whether a patient's safety had been compromised, account should be taken not just of the wording in the promotional item, but of all the circumstances. The Panel had not given due weight to the way in which the two items were used. The Panel was provided with copies of training materials and an update used by the sales force, which showed that they were appropriately trained on this issue. The Panel discounted this on the basis that promotional material had to comply with the Code in its own right and not rely on clarification or further information from representatives. Napp accepted that promotional material needed to stand alone in complying with the Code and was not appealing the Panel's ruling of a breach of Clause 3.2 in this regard. But in determining whether Napp's conduct breached Clause 2 for bringing the industry into disrepute through compromising patient safety, it would be unjust if the training programme and representatives' activities were not taken into account. Napp reiterated that its representatives were fully trained in the contraindications for the product and would have corrected any misunderstanding apparent from a discussion with GPs using the detail aid. The shorter leavepiece would only have been left with GPs who had been taken through the detail aid by a representative. This factor significantly reduced any possible risk to patients, and due weight had not been given to this.

Napp submitted that it had not received any reports of adverse reactions attributable to the use of OxyContin tablets in UK patients with moderate to severe hepatic impairment or severe renal impairment. Napp was not aware of any evidence that patients had been put at risk as a result of its promotional items.

Napp noted that Janssen-Cilag's submission for a ruling of a breach of Clause 2 was on the basis of the cumulative effect of three separate alleged breaches of the Code, namely: it not being clearly stated that OxyContin tablets should not be started until 24 hours post-operatively; it not being clear that patients with severe renal or moderate to severe hepatic impairment should not be given OxyContin tablets; and the recommendation of 40mg as a starting dose for all patients irrespective of the indication.

Napp noted that the Panel ruled a breach of the Code only in respect of the allegation about patients with renal or hepatic impairment. Napp submitted that the ruling of a breach in only one of the three areas complained of, when taken together with the points above, had not merited a ruling of a breach of Clause 2.

Napp submitted that no account had been taken of its previous record: according to its records, which dated back to 1986, it had never been ruled in breach of Clause 2 or its equivalent. Napp submitted that in the more recent past, it had only been ruled in breach of the Code once in the last three years.

Napp submitted that for these reasons, it was appealing the Panel's ruling of breach of Clause 2 of the Code. The company was simply trying to highlight those categories of patients with whom they needed to take extra care in prescribing a starting dose. Napp regretted that its wording was capable of misunderstanding but considered that the ruling of a breach of Clause 3.2 was a sufficient penalty.

COMMENTS FROM JANSSEN-CILAG

Janssen-Cilag noted Napp's submission that the claim '5mg starting dose in frail patients and those with renal and hepatic impairment' warned doctors of the advice in the SPC that for certain classes of patients they should adopt a conservative approach and should not use a 10mg starting dose. Janssen-Cilag noted that OxyContin was absolutely contraindicated in patients with moderate to severe hepatic impairment and severe renal impairment. Therefore, OxyContin was inappropriate and potentially dangerous at any dose in those groups of patients.

Janssen-Cilag did not entirely agree with Napp's submission that there was a general presumption in the Code that doctors did not need to be made expressly aware of all contraindications for a product. What was clear however, was that once a company actively promoted a medicine in a particular indication or patient group, it must clearly state any relevant absolute contraindications. That was to say, one could not make a promotional claim stating that a medicine was acceptable in patients with renal and hepatic impairment without clearly stating that the medicine was absolutely contraindicated in moderate to severe hepatic impairment and severe renal impairment. Napp had brought the industry into disrepute by not explicitly conveying the absolute contraindications when making specific promotional claims concerning patients with different degrees of renal and hepatic impairment.

Janssen-Cilag agreed with the Panel's statement that the relevant promotional items should be able to stand alone on their own merit.

Janssen-Cilag considered that the claim that a 5mg starting dose was acceptable in patients with renal and hepatic impairment should not have been made without further qualifying statements relevant to the contraindications listed in the OxyContin SPC. Representatives should not have been issued with these materials in the first instance, and therefore no amount of training or explanation could justify use of the claim. Napp was also assuming that the claim would not be seen by a health professional without prior discussion with a representative. The detail aid could be picked up by attendees at a recent meeting, without the need to discuss it with a representative.

Janssen-Cilag did not consider that the fact that Napp had no record of a specific adverse drug reaction report related to the use of OxyContin in patients with moderate to severe hepatic impairment and severe renal impairment in the UK in 2003 was an adequate defence. Lack of a reported adverse drug reaction had not excused Napp from its obligations to protect patient safety at all times. The fact that Napp had not received any adverse reports related to this issue in 2003 might be due to the vigilance of health professionals who had read the OxyContin SPC thoroughly and discounted Napp's claim of a '5mg starting dose in frail patients or those with renal or hepatic impairment', and the health professionals would instead adhere to the contraindications listed in the OxyContin SPC.

Janssen-Cilag noted that it had appealed the Panel's ruling of no breaches of Clause 2 of the Code. The specific promotion of OxyContin in patients with renal and hepatic impairment, despite the contraindications listed in the OxyContin SPC was putting patient safety at risk and was bringing the industry into disrepute, justifying a breach of Clause 2. Furthermore, the contraindications regarding the pre-operative and immediate post-operative use of OxyContin should also have been clearly stated, as was the case in other promotional materials submitted to the Panel by Napp. Napp claimed that 'GPs did not treat these patients' but this had already been stated to be incorrect. GPs did treat patients within 24 hours of their day care operations.

Janssen-Cilag requested that the Appeal Board took into account Napp's previous record of continuing to potentially endanger patient safety by not clearly qualifying certain promotional claims related to patients with moderate to severe hepatic impairment, severe renal impairment and patients in the post-operative setting, despite giving Janssen-Cilag its written assurances that it would do so.

APPEAL BY JANSSEN-CILAG

Janssen-Cilag noted Napp's view that the GP detail aid was entirely appropriate for the types of patients a GP would treat, which did not include patients who were in the immediate post-operative period. Janssen-Cilag alleged that this was an incorrect conclusion, with an inherent assumption that GPs would neither treat any pre-operative patients, nor treat patients that had been discharged within 24 hours of an operation. There were more than a million day case operations performed in England alone in 2002-2003. To then make the assumption that GPs did not treat these patients was potentially endangering the safety of a large number of patients discharged back into the community on the same day as their operation.

Janssen-Cilag alleged that it had previously raised the issue of the contraindication stating 'not recommended for pre-operative use or for the first 24 hours post-operatively' in inter-company correspondence dated May 2003, and although Napp had given written assurances that 'physicians would be made aware of all contraindications' from correspondence dated June 2003 this had clearly not happened. Janssen-Cilag stated that it had alleged a breach of Clause 2 of the Code to highlight Napp's failure to comply with its own written assurances, in addition to the continued compromise of patient safety by the manner in which Napp continued to promote OxyContin.

Additionally, Janssen-Cilag considered that the claim '75% of patients experienced pain relief by 15 minutes after a single 40mg dose' might compromise patient safety which justified a ruling of a breach of Clause 2.

COMMENTS FROM NAPP

Napp noted that Janssen-Cilag had not alleged that the failure to state that OxyContin should not be started until 24 hours post-operatively, individually warranted a ruling of breach of Clause 2. Napp argued that the cumulative effect of several alleged breaches might together compromise patient safety and bring the industry into disrepute. However, in its appeal Janssen-Cilag had changed tack and argued for the first time that each of the alleged breaches, individually, breached Clause 2. It was wrong that Janssen-Cilag should in effect be making different allegations of breach at the appeal stage. This point alone should be sufficient reason for the Appeal Board to reject Janssen-Cilag's appeal.

Napp reiterated that its GP detail aid was entirely appropriate for the types of patients treated by a GP, which did not include those who were in the immediate post-operative period. The Panel had ruled in Napp's favour on this point. Janssen-Cilag appealed, arguing that this was an incorrect conclusion because more than a million day case operations were performed in England during 2002-2003. Napp submitted that although these patients were discharged back into the community on the same day as their operation, they were not discharged without also receiving a hospital prescription for analgesics covering the immediate post-operative period and usually beyond. Day-case surgery patients were not, therefore, visiting their GPs within 24 hours of discharge and requesting prescriptions for analgesia. In support of this, Napp had conducted an Internet survey of 329 consultants who provided analgesia for day-case surgery. The consultants were from anaesthetics and intensive care, general surgery and trauma and orthopaedic surgery.

Napp showed that these consultants normally prescribed the following post-operatively: diclofenac (82%), dihydrocodeine (31%), co-codamol (26%), fentanyl (26%), paracetamol (23%), co-proxamol (23%), tramadol (21%), morphine (15%), co-dydramol (15%), ibuprofen (13%) and codeine (10%). Napp noted that although oxycodone was listed as an analgesic option, not one respondent specified it as something they normally used. OxyContin tablets, therefore, were not being prescribed by these consultants during the 24 hour post-operative period, consistent with the product's SPC and Napp's promotion. The consultants most commonly prescribed post-operative pain medication for five days (36%), followed by one week (23%), three days (21%), two weeks (10%) and four days (5%). Only 3% of respondents prescribed analgesics for just one day. However, most importantly, all of the respondents from these key specialist areas for day-case analgesia said they prescribed at least 24 hours of post-operative analgesia.

The consultants assessed each patient's requirements individually and advised them of any changes needed to the medication they had been taking in the pre-operative period. In the post-operative period, patients were discharged with a prescription for pain medication, and if this proved to be insufficient after several days, patients were generally advised to contact the day surgery unit or hospital first for advice and then to contact the GP if required. A few typical comments on this point were: 'See GP if pain not improving within 1 week'; 'Should not need to see [GP] as analgesic given is enough and therefore to phone the day unit'; 'Patients are told to ring hospital day unit for advice if pain not controlled. Then they may be told to ring GP'.

Napp submitted that based on the results of this survey day-case surgery patients were, as a matter of course, given analgesics to cover the 24 hour post-operative period (and usually beyond this), and they were not being forced to request such medication from their GPs.

Napp submitted that the claim '75% of patients experienced pain relief by 15 minutes after a single 40mg dose' had not been in breach of Clause 2 due to its very prominent starting dose information, and patient safety was not compromised.

Napp noted that Janssen-Cilag had misquoted inter-company correspondence. In its letter to Janssen-Cilag, Napp had confirmed that prescribing physicians were made aware of all contraindications for its range of preparations. The letter had not stated that prescribing physicians 'would be' made so aware, as stated by Janssen-Cilag, which implied a change needed to be made to current practice, rather, Napp had confirmed that physicians were already made aware through promotional materials appropriately tailored for the relevant audience (eg different materials for GPs and consultants) and also through discussions with Napp's representatives. Napp reiterated that its representatives were fully trained in the contraindications of OxyContin tablets and made prescribers aware of them.

FURTHER COMMENTS FROM JANSSEN-CILAG

Janssen-Cilag stated that one of the important absolute contraindications listed in the OxyContin SPC was 'not recommended for pre-operative use or for the first 24 hours post-operatively'. This was an important contraindication as OxyContin was absorbed in a bi-exponential fashion, and life threatening peri-operative complications such as respiratory depression and bowel obstruction were not readily reversed. Napp had continued to insist that GPs did not treat patients in the immediate post-operative period. The Panel on balance had accepted Napp's submission that the GP detail aid was appropriate for those patients who would be treated by a GP as neither the detail aid nor the leavepiece referred to patients in the immediate post-operative period, although both referred to post-operative pain. Janssen-Cilag alleged that Napp's argument was invalid, and that the Panel's ruling on the peri-operative contraindications needed to be overturned.

Janssen-Cilag stated that the crux of the argument was not whether these contraindications should have been explicitly stated when promoting the post-operative indication of OxyContin (ie not recommended for pre-operative use or for the first 24 hours post-operatively), but should they have been included in the GP detail aid? If a medicine was licensed for several particular indications, but within a specific indication there were some absolute contraindications, should the marketing authorization holder make health professionals aware of these

contraindications when specifically promoting the use of this medicine in this specific indication? For example, if an antihypertensive was licensed for use in pregnancy, but was contraindicated in the first trimester, the company promoting the product had an absolute duty to state this contraindication when promoting its use in pregnancy. Likewise, Napp had a licence for the use of OxyContin in the post-operative period, but there was a specific period of time where its use in the immediate pre-operative and 24 hour post-operative period was contraindicated.

Janssen-Cilag noted Napp's submission that the OxyContin post-operative detail aid (item OX03021) made it very clear that OxyContin tablets were contraindicated for 24 hours post-operatively and referred to prominent wording on pages 2 and 9 of that detail aid. It was therefore beyond reasonable doubt that these specific contraindications should be listed when OxyContin was promoted to health professionals who treated patients in the immediate pre-operative and 24 hour post-operative period.

Janssen-Cilag submitted that Napp should have included the pre-operative and 24 hour post-operative period contraindications specifically in the GP detail aid as it had done so in its post-operative detail aid.

Janssen-Cilag noted that the GP detail was used before and after the licence for OxyContin was extended in October 2003 to include the treatment of severe pain requiring the use of a strong opioid. Therefore it was very likely that patients going to have an operation might have been prescribed OxyContin without the GP having been made aware that OxyContin was contraindicated pre-operatively. Napp could potentially endanger patient safety by not including the pre-operative contraindication in its promotional materials aimed at GPs treating patients suffering from pain and who were waiting for an operation.

Janssen-Cilag noted that Napp's whole argument was based upon the presumption that GPs had not treated patients pre-operatively (this was not so, as stated above), and that GPs would not treat any patients within the immediate post-operative period. Napp had commissioned an Internet survey to defend this argument. There were several inherent potential biases associated with this kind of survey eg selection bias, no open ended questions and the issues associated with a pharmaceutical company performing its own market research. The important question to address was 'Do GPs see and treat patients in the immediate post-operative period?' It might have been more helpful if Napp had interviewed GPs.

Janssen-Cilag submitted that a cursory search of peer reviewed medical journals clearly pointed out the reality of day-case surgery. McHugh *et al* (2002) reported that up to 82% of patients sent home after day-case surgery were in pain. Medical staff had not always performed post-operative pain assessments. Some patients were sent home without any medication. Hunter *et al* (1993) stated there were patients that self-medicated (potentially with OxyContin prescribed pre-operatively by the GP). Napp's own internet survey supported this view as the answers to questions regarding existing pre-operative analgesia included the following: 'continue the same', 'continue it if regular prescription', 'to carry on with their analgesic treatment as before', 'take prescribed drugs', 'bring drugs and prescription with you', 'continue'. Advice was sought from GPs by approximately 4-11% (McHugh *et al*, Hunter *et al*) of patients in the immediate post-operative period, resulting in home visits by the GP in approximately 2.2% of cases (Hunter *et al*). This evidence therefore invalidated Napp's view that its 'GP detail aid was entirely appropriate for the types of patients treated by a GP, which did not include patients who were in the immediate post-operative period'.

Janssen-Cilag noted the Panel's comments that neither the detail aid nor the leavepiece referred to patients in the immediate post-operative period although both referred to post-operative pain. This was not the case. OxyNorm was licensed for use in the immediate post-operative period (unlike the contra-indications listed in the OxyContin SPC). The detail aid therefore had promoted the use of OxyNorm in the immediate post-operative setting as the prominent heading on the front cover stated 'for moderate to severe cancer pain or post-operative pain'. The use of OxyNorm for immediate post-operative use, and the use of OxyContin for post-operative use without any reference to a time frame, could lead a GP to conclude that the promotional claims made about OxyContin were relevant and applicable to the immediate post-operative treatment period. This conclusion was further strengthened by the fact that the claim of '75% of patients experienced pain relief by 15 minutes after a single 40mg dose' was referenced to Curtis *et al* where women were treated with OxyContin in the immediate post-operative setting.

Janssen-Cilag hoped that the evidence above would persuade the Appeal Board to accept its arguments that the specific contraindications related to the use of OxyContin in the immediate peri-operative period should have been clearly stated in the GP detail aid as they were in the post-operative detail aid.

With regard to the claim 'moderate to severe hepatic impairment contraindications' Janssen-Cilag had made Napp aware of its concerns regarding patient safety and the lack of explicitly stating several important contraindications in inter-company correspondence. Napp had argued that Janssen-Cilag had misquoted its correspondence dated June 2003 by stating 'would be' instead of 'prescribing physicians are made aware'. It was immaterial to the core issue at stake here whichever way one interpreted this statement. The fact was that Napp had not only not made physicians aware of the contraindications associated with OxyContin, but even went so far as to promote the use of OxyContin for patients with renal and hepatic impairment (including therefore the use in patients with moderate to severe hepatic impairment and severe renal impairment). Janssen-Cilag's view was that the breach of Clause 2 of the Code was correct as Napp had compromised patient safety and brought discredit upon and reduced confidence in the pharmaceutical industry.

Janssen-Cilag, in summary, urged the Appeal Board to uphold the Panel's ruling of a breach of Clause 2 with regard to the active promotion of OxyContin for the use in patients with any degree of renal and hepatic

impairment. Janssen-Cilag urged the Appeal Board to overturn the Panel's ruling with regard to the lack of the explicit contraindications when OxyContin was promoted in the peri-operative setting. The issue was not whether the contraindications should have been explicitly stated when OxyContin was promoted in the pre-operative and post-operative setting as was clearly demonstrated in the post-operative detail aid, but whether GPs treated and advised patients during this time period. There was evidence that this was the case, and Janssen-Cilag alleged that Napp was therefore in breach of Clause 2 of the Code by not having clearly stated these contraindications in the GP detail aid.

APPEAL BOARD RULING

The Appeal Board noted that Janssen-Cilag had complained that the cumulative effect of a number of issues relating to patient safety had been worthy of a ruling of a breach of Clause 2 of the Code. These issues related to the fact that OxyContin was contraindicated within the first 24 hours post-operatively and in patients with severe renal or moderate to severe hepatic impairment. Janssen-Cilag had considered that these contraindications had not been made sufficiently clear in the material at issue. Janssen-Cilag had also alleged that the failure to clearly state that 40mg was not a recommended starting dose was also prejudicial to patient safety (see point 2 above).

The Appeal Board noted that the Panel had separated Janssen-Cilag's reasons for the alleged breach of Clause 2 such that it had ruled a breach of Clause 2 of the Code with regard to the issue concerning patients with renal or hepatic impairment but no breach of Clause 2 with regard to the other two reasons. The Appeal Board noted that the Panel had separated the reasons in order that each party would have the opportunity to appeal. The Appeal Board did not consider itself bound by this separation of the issues. The Appeal Board noted Napp's submission on this point and that Janssen-Cilag's appeal was in response to the Panel's rulings.

The Appeal Board was particularly concerned that the claim '5mg starting dose in frail patients or those with renal or hepatic impairment' gave the impression that patients with any degree of renal or hepatic impairment could be treated with OxyContin which was not so. Patients with either severe renal or moderate to severe hepatic impairment should not be treated with OxyContin at all.

With regard to the issue of post-operative use of OxyContin the Appeal Board noted that such use was referred to a number of times without qualification. 'For moderate to severe cancer or post-operative pain' was a heading on the front cover of the detail aid and a strapline on pages 3 and 5. The Appeal Board was concerned that it had not been made clear that post-operative pain in the first 24 hours after an operation could not be treated wth OxyContin.

The Appeal Board also noted its ruling in point 2 above that the claim '75% of patients experienced pain relief by 15 minutes after a simple 40mg dose' did not make it sufficiently clear that 40mg was not an appropriate starting dose.

Overall the Appeal Board considered that the detail aid and the leavepiece might lead to prescribing in patients for whom the product was contraindicated which might compromise patient safety and such advertising brought discredit upon and reduced confidence in the pharmaceutical industry. The Appeal Board thus ruled a breach of Clause 2.

4 Claim for 3.9% incidence of constipation

Page 5 of the detail aid was headed 'Very well tolerated' and referred to adverse event data from 5 studies involving 2,199 patients using OxyContin tablets. A bar chart gave the percentage of complaints of nausea (5.3%), vomiting (2.6%) and constipation (3.9%). A footnote to the constipation data stated 'Two thirds of patients suffering constipation received a laxative. Prophylactic laxatives should always be considered with strong opioid treatment'. The data was referenced to 'data on file'.

COMPLAINT

Janssen-Cilag noted that the data was from a post-marketing surveillance study performed in Germany. The majority of these patients were not treated in accordance with the terms of the UK marketing authorization.

The constipation rate reported in this population of patients did not reflect the current available data from trials in the current licensed indications for OxyContin. The constipation rates for OxyContin quoted in the supporting literature were 21% in a randomised, double-blind, controlled study in cancer patients (Mucci-LoRusso *et al* 1998) and 30% in a long-term, open-label trial in cancer patients (Citron *et al* 1998) with a 49% discontinuation rate in this study.

Janssen-Cilag alleged that the claim for a low rate of constipation was in breach of Clause 7.2 and that the claim 'Very well tolerated' was exaggerated in breach of Clause 7.10 of the Code.

RESPONSE

Napp acknowledged that a majority of the patients were not treated within the terms of the UK marketing authorization until the indication was extended on 28 October 2003 and so it had not used the study to support efficacy claims. However, side effects of strong opioids occurred independently of indication. This was not a clinical trial; it was a post-marketing survey of the use of OxyContin in actual clinical practice, which might explain the different constipation rates. Therefore, it reflected the results achieved in real clinical practice.

The 3.9% claim appeared in a box along with asterisked wording clarifying that two-thirds of patients suffering with constipation received a laxative. It further stated that prophylactic laxatives should always be considered with strong opioid treatment. This was appropriate advice, reflecting best clinical practice, aimed at minimising the risk of well recognised side effects of treatment with opioids.

While Janssen-Cilag argued that the study population ought to have been treated in line with the UK

marketing authorization if Napp was to use this study in support of any claims, the two clinical trials referred to by Janssen-Cilag as showing constipation rates for OxyContin of 21% and 30% also could be said to refer to a patient population that was only a subset of the UK marketing authorization. Both studies concerned cancer patients, and at the time these materials were in use, the licensed indication included both cancer and post-operative patients. Therefore, these two studies also were not wholly representative of patients treated within the terms of the UK marketing authorization. Again, Napp did not consider this mattered, as side effects of strong opioids were well known and did not change significantly based on the indication for which they were used.

Janssen-Cilag's reference to a 30% constipation rate in Citron *et al* was, itself, misleading. Under the heading of safety, the study reported that constipation decreased from 30% to 10% among patients completing all 12 weeks of the study. Janssen-Cilag had not mentioned this point. Taking this into account, together with the prophylactic use of laxatives in the German post-marketing surveillance study, explained much, if not all of the variance in constipation rates between the studies.

Napp contended that claims about rates of constipation did not rise to the level of 'compromising patient safety'.

PANEL RULING

The Panel noted that the page referred to tolerability with the data originating from a post-marketing surveillance study in Germany. The data on file, to which the results were referenced, stated that the indications in Germany were different from those in the UK. Fifty seven percent of patients had pain as a consequence of musculoskeletal disease, 33% had pain caused by cancer, 13% had pain caused by disease of the nervous system and 24% had pain from other illnesses. Constipation was reported by 85/2199 patients; 38 of the 59 patients who reported constipation at the first visit and 34 of 51 patients who reported constipation at their second visit received medical treatment. The Panel accepted Napp's submission that the side effects of strong opioids were well known and did not change significantly depending on the indication for which they were used.

The OxyContin SPC stated that constipation was a common event (incidence of ≥1%). Citron *et al* reported that for patients who completed 12 weeks of the study (n=88) constipation decreased from 30% to 10%; concomitant therapy was reported to be an important factor in this decrease. Mucci-LoRusso *et al* reported a constipation rate of 21% in a 12 day trial of oxycodone.

The Panel noted that the page did not make a claim for a low rate of constipation. The figure of 3.9% was not inconsistent with the limited data in the SPC. Published clinical studies gave rates of 21% and 30% dropping to 10% after 12 weeks of treatment. The Panel was, however, concerned that the categorical figure of 3.9% did not reflect the balance of the evidence. The Panel thus ruled a breach of Clause 7.2 of the Code. This ruling was not appealed.

The Panel did not consider that the heading to the page 'Very well tolerated' in association with the data for constipation was exaggerated as alleged. No breach of Clause 7.10 of the Code was ruled. This ruling was appealed by Janssen-Cilag.

APPEAL BY JANSSEN-CILAG

Janssen-Cilag noted the claim 'Very well tolerated' was derived from a single post-marketing surveillance study (n=2,199) (Napp data on file) and not from 5 studies as claimed in the detail aid. To be able to make the claim Napp would have to prove that OxyContin was indeed always very well tolerated and that 3.9% was a true and accurate reflection of the available evidence. The Panel had already ruled that the figure of 3.9% (with respect to the constipation rate) was not a fair and accurate reflection of the evidence available.

Janssen-Cilag alleged that the true incidence of constipation was likely to be in excess of 20%, and as such Napp could not substantiate the exaggerated claim of 'Very well tolerated'. Additionally, the OxyContin SPC had 29 common and 51 uncommon side effects listed. Allowing the claim 'Very well tolerated' in the face of a large number of common (1-10% frequency) adverse events in the SPC seemed perverse.

Janssen-Cilag reiterated its comments that the figure of 3.9% was taken from data that Napp had admitted was derived from patients of whom approximately two thirds were not treated in accordance with the UK marketing authorization.

Janssen-Cilag stated that Napp's submission that the side effects of strong opioids were well known and did not change significantly depending on the indication for which they were used was only partially correct, as there was a difference in the incidences of dose dependent side effects. A person given 0.1mg of morphine would develop less constipation compared to a person given a daily dose of 100mg.

Janssen-Cilag noted that cancer patients on average consumed higher dosages of oxycodone compared to those patients being treated for a non-cancer indication (DIN-LINK Report for oxycodone MAT, December 2003). Therefore it was also reasonable to conclude that patients with different underlying medical conditions being prescribed OxyContin would receive different daily doses and constipation rates would therefore also differ. This difference was illustrated by comparing the incidence of constipation reported in the post-marketing surveillance study in which the majority of patients did not have cancer, with the incidence described in the study by Citron *et al* (3.9% vs 30% respectively). In Citron *et al*, 3% of the patients, where action was taken for common opioid associated adverse events, had their medication doses revised downwards to reduce constipation. It was therefore fair to conclude that constipation was dose dependent and to state that 'side effects of strong opioids occur independently of indication' was only partly true. The therapeutic indications did matter and the side effect data from one indication could not be readily extrapolated to another.

COMMENTS FROM NAPP

Napp noted that Janssen-Cilag had appealed the Panel's ruling of no breach of the Code with regard to the claim 'Very well tolerated' because the OxyContin SPC listed 29 common (1-10% frequency) adverse events and the true incidence of constipation was likely to be in excess of 20%. The Panel had found that the 3.9% rate of constipation had not reflected the balance of the evidence and ruled a breach of Clause 7.2 of the Code, which Napp had accepted. Nevertheless, the Panel had not considered that the heading to the page 'Very well tolerated' in association with the data for constipation was exaggerated as alleged.

Napp noted that the OxyContin SPC listed various adverse reactions in section 4.8, and these were shown in a table format divided into columns for 'Common' and 'Uncommon' reactions. This listing was in accordance with the European Commission's Guideline on how to present information in SPCs including adverse event information. The Guideline was not legally binding, but Napp had followed it in preparing or amending SPCs since that date, including those for OxyContin.

Napp noted that the Guideline required 'comprehensive information on all adverse reactions attributed to the medicinal product with at least reasonable suspicion'. This resulted in fuller listings of adverse events than was the case before the Guideline was issued, when only clinically significant events were listed.

Napp noted that the listing for OxyContin tablets was a comprehensive reflection of adverse events that had been reported in clinical studies and during clinical use of the product. A number of these adverse events, although common, would be considered by most doctors and patients to be relatively minor in nature, such as sweating, dry mouth and pruritis. It was notable that no 'very common' adverse events were listed in the OxyContin SPC, which meant that none of the adverse events (including constipation) was reported as being experienced more frequently than 10%.

Napp submitted that the listing of adverse events in the SPC was simply to comply with the SPC Guideline and could not be used to argue that OxyContin tablets were not well tolerated. By way of comparison, Janssen-Cilag's SPC for Evra, its contraceptive patch, which followed the Guideline, listed in section 4.8, 32 common, 60 uncommon and 51 rare adverse events.

Napp noted Janssen-Cilag's submission that the true incidence of constipation was likely to be in excess of 20% on the basis that 3.9% was an understatement and that it was based on a study in which only 33% of the patients were treated in accordance with the UK marketing authorization (as it was before October 2003 – all of the patients in the study would fall within the current licensed indication). Janssen-Cilag had claimed that this was significant because 'cancer patients on average consumed higher dosages of oxycodone compared to those patients being treated for a non-cancer indication'.

Napp submitted that the 3.9% rate of constipation was clearly referenced to alert the reader to the fact that two thirds of patients in the study had received a laxative. Had none been treated with a laxative, the constipation rate would probably have been higher. However, the point which was also made in the detail aid was that prophylactic use of laxatives should always be considered with any strong opioid treatment. This was in accordance with good clinical practice, as witnessed by the extracts from palliative care textbooks and journals. It was also in line with the recommendation in the OxyContin SPC which stated in section 4.8 that 'Constipation may be prevented with an appropriate laxative'. The point being made in the detail aid was that when this practice was followed, the rate of constipation would be low.

Napp submitted that Janssen-Cilag had relied on Citron *et al* to support its argument that the rate of constipation was in excess of 20% pointing out that 3% of patients had their medication doses revised downwards to reduce constipation and claimed that the study showed that constipation rates could increase as the dosage was increased.

Napp noted the Panel's comment that after 12 weeks (and the use of laxatives) constipation in this study decreased from 30% to 10%. Significantly, Citron *et al* stated that 'concomitant therapy, particularly for constipation, was an important factor in the decrease of the number of reports of adverse events over time' and that 'the acceptability rating suggests that the adverse events experienced were tolerable and did not worsen over the course of the study despite the significant increase in total daily dose of oxycodone' and finally, that 'constipation can be managed prophylactically with laxatives'.

Napp submitted that contrary to Janssen-Cilag's argument, Citron *et al* showed that constipation rates decreased in spite of increasing dosage levels, due to the use of laxatives. The authors concluded that adverse events were tolerable, and this supported, rather than undermined, the claim that OxyContin was very well tolerated.

Napp noted Janssen-Cilag's other argument, as mentioned above, was that 'cancer patients on average consume higher dosage levels of oxycodone compared to those patients being treated for a non-cancer indication'. This claim was referenced to a DIN-LINK report from CompuFile. Napp submitted that Janssen-Cilag's analysis of the DIN-LINK data was flawed in several important respects.

Napp noted that above a table provided with its appeal Janssen-Cilag stated 'Problems will occur if patients were moving swiftly through the doses, but this was not felt to be a major issue with this particular data'. Napp submitted that its analysis showed this was a major problem with this data.

Napp submitted that in the dataset entitled 'Total Diagnoses', the patient records total 360 records (by adding the numbers of patients listed against each dosage strength). But this data was based on a sample of just 223 patients in total. 360 records from 223 patients suggested a considerable level of movement through the doses during this period. Also the average number of prescriptions per patient was greater at the sub-total level than it was at each individual strength. This would only happen if patients were moving up through the individual

doses. Napp had checked this with the company which had provided the data to Janssen-Cilag. If, for example, a patient was prescribed OxyContin 40mg tablets for 4 weeks, but within 1 week his doctor increased his dosage to 80mg tablets and again prescribed it for 4 weeks, the dataset would record 1 week of 40mg, 3 weeks of 40mg and 80mg and 1 week of 80mg. In other words, there would be significant double-counting where patients were prescribed a stronger dose before current prescriptions had been used up. A further problem with Janssen-Cilag's data was the double-counting of cancer patients in the two datasets. Cancer patients were included not only in the dataset entitled 'Prob/Notes: Total Diagnoses' dataset but also in the dataset entitled 'Cancer'.

Napp submitted that leaving the issues with the data to one side, a closer examination revealed that the data gave little support to Janssen-Cilag's claim that cancer patients on average consumed higher dosage levels of oxycodone than non-cancer patients. A comparison of the 'Total Diagnoses' and 'Cancer' tables showed no significant difference in 'Avg mg/day' between the 5mg, 10mg, 20mg or 40mg strengths, which accounted for 85% of the patient records (not allowing for any double-counting). The only difference was for the 80mg strength. However, this difference was largely the result of 2 patients on exceptionally high doses.

Napp submitted that a synopsis of all patients in the dataset who were treated with at least one oxycodone modified release prescription in 2003 showed that there were two cancer patients whose dosages were unusually large. One took 720mg/day every month and the other 480mg/day over the same period. Just these 2 patients contributed 22% of the total oxycodone cancer prescriptions recorded in the dataset for 2003.

Napp submitted that the two exceptionally high-dose patients skewed the data and when they were excluded from the database, the difference in 80mg dosage per day between the 'Cancer' and 'Total Diagnoses' categories fell substantially from 117mg/day (oxycodone) and 75mg/day (OxyContin) to 48mg/day (oxycodone and OxyContin combined). This was shown in Napp's reworking of Janssen-Cilag's schedule to exclude the two high-dose patients (using Napp's definition of cancer patients and product axis and with branded and generic combined, as there was no generic equivalent to OxyContin tablets). This also demonstrated a significant reduction in the difference in average dosage per day between the 'Total Diagnoses' and 'Cancer' categories, from 39mg/day down to 10mg/day. The company which had provided Janssen-Cilag with the data had seen and approved this statement about the DIN-LINK data.

In conclusion Napp submitted that it was puzzled as to why Janssen-Cilag had appealed; it had largely rehashed arguments it had made in its complaint, which were carefully considered and dismissed by the Panel. To the extent that Janssen-Cilag had introduced new data, Napp submitted that it had showed why such data had not supported Janssen-Cilag's arguments. Napp asked the Appeal Board to reject Janssen-Cilag's appeal.

FURTHER COMMENTS FROM JANSSEN-CILAG

Janssen-Cilag stated that it maintained its arguments that OxyContin with 29 common and 51 uncommon side effects could potentially be promoted as well tolerated, as illustrated on the back cover of the Napp GP detail aid, if this was a common class effect occurrence. The use of 'very', however, implied that OxyContin had a special merit or was especially well tolerated, and this was not so. The company repeated its claim that a product with a constipation rate of in excess of 10% (if not treated with laxatives), the fact that 49% of patients dropped out of Citron *et al*, the fact that 3% of patients in this study had their doses revised downwards to reduce constipation, and with 80 listed side effects could not be classified as very well tolerated.

Janssen-Cilag disagreed with Napp's selective elimination of a number of patients from the DIN-LINK data. Napp had not eliminated any outliers in the non-cancer group, apart from the issue of moulding the data to suit its needs.

Janssen-Cilag urged the Appeal Board to overturn the Panel's ruling that OxyContin could be classified as very well tolerated.

APPEAL BOARD RULING

The Appeal Board noted that in its complaint Janssen-Cilag had linked the claim 'Very well tolerated' to the constipation data and alleged that the claim was exaggerated. At the appeal hearing Janssen-Cilag acknowledged that it had expanded its allegation to refer to adverse events other than constipation. The Appeal Board considered that this went beyond the original complaint.

The Appeal Board noted that the constipation data depicted was from a post-marketing surveillance study. The Appeal Board was concerned that data from such a study, which relied on spontaneous reporting of adverse events, had been used as the basis for a safety claim. The Appeal Board considered that 'Very well tolerated' was a strong claim. The Appeal Board considered that given the constipation data the claim 'Very well tolerated' was exaggerated as alleged and a breach of Clause 7.10 was ruled. The appeal on this point was successful.

During its consideration of this matter the Appeal Board was most concerned that the page in question, headed 'Very well tolerated' was tagged *inter alia* 'Tolerability'. In the Appeal Board's view such a tag might lead a reader to assume that the data depicted related to overall tolerability whereas only results relating to nausea, vomiting and constipation were shown. The Appeal Board was also concerned that the page failed to state that the data was from a post-marketing surveillance study. The Appeal Board's requested that Napp be advised of its concerns.

Complaint received **5 January 2004**

Case completed **10 May 2004**

CASE AUTH/1545/1/04

PRIMARY CARE TRUST HEAD OF PRESCRIBING AND PHARMACY SERVICES v GLAXOSMITHKLINE

Glitazone guidelines

The head of prescribing and pharmacy services at a primary care trust (PCT) complained about 'Guidelines for the use of thiazolidinediones' which had been distributed by a representative of GlaxoSmithKline. The guidelines were printed on headed notepaper from the local hospitals NHS trust and the first page referred to thiazolidinediones generally. A 'Treatment pathway' was printed on the reverse and showed that where either a sulphonylurea in patients of normal weight, or metformin in obese patients, failed to control type 2 diabetes then rosiglitazone 4mg once daily should be used. Rosiglitazone (GlaxoSmithKline's product Avandia) was the only thiazolidinedione referred to by name.

The complainant noted that the guidelines had been distributed to GP practices in the area and local community hospitals. The local PCT was unaware that the hospital had produced such guidelines and on enquiry it appeared that someone had misappropriated the NHS trust's logo and address and photocopied the guidelines on to its headed paper. Senior figures at the hospital were very concerned at bogus guidelines being distributed.

The Panel was concerned about the way in which the guidelines had been produced. They had originally been prepared by a diabetes nurse as supporting material for a primary care meeting. The nurse was employed by the trust. The nurse's salary was supported by an unrestricted grant from GlaxoSmithKline to the trust and the meeting, although organised by the nurse, was supported by GlaxoSmithKline through the provision of refreshments. The Panel expressed concern with regard to the impression that this arrangement could create but noted that the meeting was not the subject of the complaint.

The Panel considered that the representative's decision to have the NHS trust letterhead photocopied on to the guidelines and then to distribute them without the prior approval of GlaxoSmithKline meant that the representative had not maintained a high standard of ethical conduct; breaches of the Code were ruled. The Panel considered that the presentation of the guidelines, on NHS trust notepaper, gave the impression that they represented official local policy which was not so. The title 'Guidelines for the use of thiazolidinediones' implied that the document was about thiazolidinediones in general although the treatment pathway referred only to rosiglitazone ie GlaxoSmithKline's product Avandia. The Panel thus considered that when distributed by a representative of GlaxoSmithKline the guidelines were disguised promotion for Avandia. A breach of the Code was ruled.

The Panel considered that the conduct of the representative brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

As is usual with all cases settled at Panel level, a report was made to the Code of Practice Appeal Board. The Appeal Board was concerned about this case. It decided in accordance with Paragraph 12.1 of the Constitution and Procedure to report the company to the ABPI Board of Management for it to decide whether further sanctions should be applied.

The ABPI Board noted that this case had resulted from a serious error of judgement by a GlaxoSmithKline representative who had acted without company approval. The Board decided that as GlaxoSmithKline had taken prompt firm action with the individual and others to reinforce compliance with the Code to ensure the serious error did not recur, no further action was necessary.

The head of prescribing and pharmacy services at a primary care trust (PCT) complained about some diabetes treatment guidelines which had been distributed by a representative of GlaxoSmithKline UK Ltd.

The guidelines consisted of a single A4 sheet and were printed on headed notepaper of the local hospitals NHS trust. The document was headed 'Guidelines for the use of thiazolidinediones' and the first page referred to the class of medicines generally. A 'Treatment pathway' was printed on the reverse and showed that where either a sulphonylurea in patients of normal weight, or metformin in obese patients, failed to control type 2 diabetes then rosiglitazone 4mg once daily should be used. Rosiglitazone (GlaxoSmithKline's product Avandia) was the only thiazolidinedione referred to by name.

COMPLAINT

The complainant noted that the guidelines had been laminated and bore the logo of the local hospitals NHS trust; they had been distributed to GP practices in the area and local community hospitals. The local PCT was unaware that the hospital had produced such guidelines and on enquiry it appeared that someone had misappropriated the NHS trust's logo and address and photocopied the guidelines on to its headed paper.

The complainant noted that the only product mentioned was rosiglitazone. The medical director at the hospital, together with the local diabetologists and the chief executive, were very concerned at bogus guidelines being distributed.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to Clauses 2, 9.1, 10.1 and 15.2 of the Code.

RESPONSE

GlaxoSmithKline stated that the guidelines were not wholly unconnected with the local hospitals NHS trust, inasmuch as they were prepared by a diabetes

specialist nurse in the employ of the trust, the salary being supported by an unrestricted grant from the company. The documentation was produced as supporting material for a primary care meeting. To the best of GlaxoSmithKline's knowledge, the documentation was seen and tacitly approved by the local diabetes consultant prior to this meeting and as written reflected current practice within the local district general hospital, although no 'official' departmental diabetes guidelines had been generated to date.

GlaxoSmithKline stated that the meeting in question was organised by the diabetes nurse. It was not sponsored by the company although refreshments were provided by the local representative. At the meeting, copies of the document were requested by several of the delegates, and the representative considered that the guidelines might be of wider interest. At that time the guidelines were on plain A4 paper with no letterhead. Subsequently, at the instigation of the representative, the diabetes nurse photocopied the local hospitals NHS trust letterhead on to the original document, which was then laminated and distributed to some 40-45 general practitioners and practice nurses before it was withdrawn.

The representative's decision to reproduce and distribute the document incorporating the trust letterhead was clearly a serious error of judgement. Whilst GlaxoSmithKline did not consider that there was any deliberate attempt to deceive, the impression could easily have been given that the guidelines were officially approved by the trust, which was not the case. Furthermore, the document had not been submitted for in-house approval by the relevant signatories, representing a breach of standard operating procedures. If it had been submitted, such a document would not have been approved for distribution.

GlaxoSmithKline accepted that, on this occasion, the high standards of conduct and judgement expected from its representatives, and mandated by Clause 15.2 of the Code, were not met. The company took such matters very seriously and formal disciplinary proceedings had been initiated.

GlaxoSmithKline did not consider that the guidelines constituted disguised promotion. The guidelines on one side of the document referred to the class as a whole rather than any individual product. The flow-chart on the reverse specifically referred to rosiglitazone but, as mentioned above, was prepared independently, and reflected actual practice at the hospital.

PANEL RULING

The Panel was concerned about the way in which the guidelines had been produced. The guidelines had originally been prepared by a diabetes nurse as supporting material for a primary care meeting. The nurse's salary was supported by an unrestricted grant from GlaxoSmithKline and the meeting, although organised by the nurse, was supported by GlaxoSmithKline through the provision of refreshments. The meeting was not the subject of complaint and it was unclear as to the exact role played by GlaxoSmithKline's representative in the proceedings. The Panel was concerned over the impression which could be given by a health professional sponsored by an unrestricted company grant and the sales representative of that company both taking part in the same meeting. In such circumstances companies must ensure that the arrangements complied with the Code and did not compromise the sponsored individual in terms of their own professional code of conduct.

The Panel noted that the representative had distributed a set of treatment guidelines without having first had them approved for use by the company. The material was being used for a promotional purpose. The representative was thus using material which had not been certified as required by Clause 14 of the Code.

The Panel considered that the representative's decision to have the NHS trust letterhead photocopied on to the guidelines and then to distribute them without the prior approval of GlaxoSmithKline meant that the representative had not maintained a high standard of ethical conduct; breaches of Clauses 9.1 and 15.2 were ruled. The Panel considered that the presentation of the guidelines, on NHS trust notepaper, gave the impression that they represented official local policy which was not so. The title 'Guidelines for the use of thiazolidinediones' implied that the document was about thiazolidinediones in general although the treatment pathway referred only to rosiglitazone ie GlaxoSmithKline's product Avandia. The Panel thus considered that when distributed by a representative of GlaxoSmithKline the guidelines were disguised promotion for Avandia. A breach of Clause 10.1 was ruled.

The Panel considered that the conduct of the representative brought discredit upon, and reduced confidence in, the pharmaceutical industry. A breach of Clause 2 was ruled.

During its consideration of this case the Panel noted point 1 (vi) of the supplementary information to Clause 18.1, Provision of Medical and Educational Goods and Services, stated that 'Health professionals should not be involved in the promotion of specific products'. The Panel queried whether the nurse should have produced the guidelines in the first place given that the treatment pathway referred only to rosiglitazone. The Panel was further concerned the nurse had collaborated with the representative, and although at the representative's instigation, had agreed to copy the NHS trust letterhead on to the guidelines. The Panel requested that GlaxoSmithKline be advised of its concerns.

APPEAL BOARD

As is usual with all cases settled at Panel level, a report was made to the Code of Practice Appeal Board. The Appeal Board was concerned about this case noting that GlaxoSmithKline had been ruled in breach of Clauses 2, 9.1, 10.1 and 15.2. It decided in accordance with Paragraph 12.1 of the Constitution and Procedure to report the company to the ABPI Board of Management for it to decide whether further sanctions should be applied.

REPORT TO THE ABPI BOARD OF MANAGEMENT

The ABPI Board noted that this case had resulted from a serious error of judgement by a GlaxoSmithKline representative who had acted without company approval. GlaxoSmithKline had accepted the breaches of the Code and had taken disciplinary action. The company acknowledged the seriousness of the error.

In addition the individual and other employees had received further training and a reminder had been sent to the sales force.

The Board decided that as GlaxoSmithKline had taken prompt, firm action with the individual and others to reinforce compliance with the Code to ensure the serious error did not recur, no further action was necessary.

Complaint received	**5 January 2004**
Case completed	**11 February 2004**
PMCPA proceedings completed	**11 March 2004**
ABPI Board proceedings completed	**18 May 2004**

CASE AUTH/1547/1/04

PROCTER & GAMBLE v IVAX

Promotion of Mesren

Procter & Gamble complained about launch materials for Mesren MR issued by Ivax. A 'Dear Customer' letter sent primarily to pharmacists, and an advertisement, informed readers that with the introduction of Mesren MR there were now three oral mesalazine 400mg products available; Asacol MR supplied by Procter & Gamble, Ipocol supplied by Lagap and Mesren MR. Both the letter and the advertisement reviewed dissolution data for all three products and considered their interchangeability.

Procter & Gamble was concerned that the claim 'Mesren, however, has a virtually identical dissolution profile and an identical qualitative formula to Asacol and can therefore be interchanged with confidence' implied that the two products were clinically equivalent. The claim of interchangeability was supported solely by non-clinical data. *In vitro* dissolution profiles and qualitative formulae were only two factors that might impact clinical interchangeability. In the absence of results from a suitably designed clinical trial, there were insufficient data to substantiate this claim for modified-release products.

This claim of interchangeability was also contrary to guidance from several well-respected publications, which clearly stated that oral mesalazines should not be considered interchangeable and should be prescribed by brand name.

In addition, Forbes *et al* (2003) made it clear that *in vitro* evidence was insufficient to demonstrate interchangeability of modified-release products. Procter & Gamble alleged that it was unacceptable to promote Mesren as a product which might be 'interchanged with confidence' with Asacol.

The Panel noted that in the 'Dear Customer' letter a figure showed marked *in vitro* degradation of the coating of Ipocol tablets compared to both Mesren MR and Asacol tablets which each showed no visible disintegration at pH 6.4. A subsequent graph compared the *in vitro* dissolution profiles of Mesren, Asacol and Ipocol at pH 7.2. Asacol and Mesren had very similar dissolution profiles whilst that for Ipocol was quite different. The letter noted that a prescription for 'Mesalazine 400mg tablets' could be filled with Mesren, Asacol or Ipocol and went on to state that if a patient had been receiving Asacol, it did not seem advisable to switch them to Ipocol, considering the significantly different *in vitro* dissolution profiles. The letter continued by stating that 'Mesren, however, has a virtually identical dissolution profile and an identical qualitative formula to Asacol and can therefore be interchanged with confidence'. This claim also appeared in the advertisement which was headed 'Interchangeability of Oral Mesalazines' and similarly reviewed *in vitro* dissolution data for all three products and considered their interchangeability.

The Panel noted the similarity of the *in vitro* dissolution profiles for Mesren and Asacol. The parties had submitted, however, that *in vitro* dissolution profiles and qualitative formulae were only two factors which might impact on clinical interchangeability. The BNF September 2003 stated that 'The delivery characteristics of enteric-coated mesalazine preparations may vary; these preparations should not be considered interchangeable'. The Panel noted, however, that only two 400mg modified-release preparations were listed in that edition of the BNF, Asacol and Ipocol; Mesren MR had not been launched at that time.

The Panel noted Ivax's submission that the claim at issue was intended to inform a pharmacist that a prescription for mesalazine 400mg modified release could be filled with either Mesren MR or Asacol. In the Panel's view, however, the claim went further than that. The claim regarding the interchangeability of Mesren and Asacol had been immediately preceded by a reference to switching patients from Asacol to Ipocol. The Panel considered that in the context in which it appeared the claim that Asacol and Mesren 'can therefore be

interchanged with confidence' was not limited to a pharmacist's dispensing choices when faced with a generically written prescription from a newly diagnosed patient, it implied that Mesren MR could be given to patients who had previously received Asacol ie the two products were clinically equivalent. There was no clinical data to show that this was so. The Panel considered that the letter and advertisement were misleading in this regard and could not be substantiated. A breach of the Code was ruled in respect of each item. Upon appeal by Ivax the Appeal Board upheld the Panel's rulings of breaches of the Code.

Procter & Gamble Pharmaceuticals UK Limited complained about launch materials for Mesren MR (mesalazine 400mg, modified-release) issued by Ivax Pharmaceuticals UK Limited. A 'Dear Customer' letter (ref IV/ME/LET/11/03), sent primarily to pharmacists, and an advertisement taking the form of an advertorial in The Pharmaceutical Journal, 6 December 2003 (ref IV/ME/AD/11/03) informed readers that with the introduction of Mesren MR there were now three oral mesalazine 400mg products available; Asacol MR supplied by Procter & Gamble, Ipocol supplied by Lagap Pharmaceuticals and Mesren MR. Both the letter and the advertisement reviewed dissolution data for all three products and considered their interchangeability.

COMPLAINT

Procter & Gamble was concerned over claims regarding the interchangeability of Asacol and Mesren MR, in particular the claim 'Mesren, however, has a virtually identical dissolution profile and an identical qualitative formula to Asacol and can therefore be interchanged with confidence' which implied that the two products were clinically equivalent. Procter & Gamble alleged that the claim of interchangeability, supported solely by non-clinical data, breached Clauses 7.2 and 7.4 of the Code.

Procter & Gamble referred to the supplementary information to Clause 7.2 'the use of data derived from in-vitro studies, studies in healthy volunteers and in animals. Care must be taken with the use of such data so as not to mislead as to its significance. The extrapolation of such data to the clinical situation must only be made where there is data to show that it is of direct relevance and significance'.

It was inappropriate to extrapolate these *in vitro* dissolution data to the clinical situation to support the message of implied clinical equivalence.

In a letter to Procter & Gamble dated 13 January 2004, Ivax stated that Procter & Gamble had used *in vitro* data in the past to support claims of non-interchangeability between Asacol and Ipocol (another oral modified-release mesalazine preparation). Procter & Gamble acknowledged that there was a theoretical link between *in vitro* dissolution data and clinical behaviour for oral mesalazine modified-release preparations. A dissimilar *in vitro* dissolution profile might therefore indicate that there might be clinical differences between two formulations. The Panel had ruled upon this Procter & Gamble claim (Case AUTH/1499/7/03) and ruled no breach.

However, the use of *in vitro* dissolution data to conclusively state that two products might be 'interchanged with confidence' (implying clinical equivalence) was an unacceptable extrapolation of *in vitro* data. Such claims, especially in the case of modified-release products, could only be supported by data from robust comparative clinical efficacy trials. Ivax stated in a letter to Procter & Gamble, dated 13 January 2004, that it considered Mesren and Asacol to be interchangeable based on the combination of 'identical qualitative formula' and comparative *in vitro* dissolution profiles.

In vitro dissolution profiles and qualitative formulae were only two factors that might impact clinical interchangeability. In the absence of results from a suitably designed clinical trial, there were insufficient data to substantiate this claim for modified-release products.

This claim of interchangeability was also contrary to guidance from several well-respected publications, which clearly stated that oral mesalazines should not be considered interchangeable and should be prescribed by brand name. For example, the British National Formulary (BNF) stated that: 'The delivery characteristics of enteric-coated mesalazine preparations may vary; these preparations should not be considered interchangeable'.

In addition, Forbes *et al* (2003) made it clear that *in vitro* evidence was insufficient to demonstrate interchangeability of modified-release products: 'Unless an alternative formulation of a modified-release product matches that of a reference product in every particular aspect of its *in vitro* and *in vivo* performance, prescribing by the proprietary name should be mandatory'.

Procter & Gamble alleged that it was unacceptable to promote Mesren as a product which might be 'interchanged with confidence' with Asacol.

RESPONSE

Ivax strongly refuted that there was any implication that the two products were clinically equivalent. The promotional materials were directed at fully-trained professionals (in this case primarily pharmacists but potentially also GPs) and it would be for them to form their own opinion as to the therapeutic value of identical dissolution profiles and identical qualitative formula.

The dissolution data was specifically described as *in vitro* and there was no attempt to mislead as to its significance. There was no dispute as to the fact that Mesren had an identical qualitative formula to Asacol. Ivax did not therefore believe that this claim was in breach of Clauses 7.2 or 7.4 of the Code.

Ivax agreed with that *in vitro* dissolution profiles and qualitative formulae were only two factors that might impact clinical interchangeability but noted that it was not claiming clinical equivalence.

There was no attempt to extrapolate the *in vitro* dissolution data to a clinical situation to support a message of clinical equivalence. Procter & Gamble's assertion that the words 'can therefore be

interchanged with confidence' equated to a claim of clinical equivalence seemed a particularly strained interpretation for any reader, not least the qualified professional reader as was the case here. The intended meaning of these words (which were aimed primarily at pharmacists) was that a pharmacist should not be concerned with filling a prescription for mesalazine with Mesren and not limit his dispensing to Asacol.

Procter & Gamble had itself used *in vitro* dissolution data to support claims of non-interchangeability between Asacol and Ipocol, yet it claimed that the same use of *in vitro* dissolution data by Ivax to (in part) support interchangeability was not valid. It seemed inequitable that Procter & Gamble should be able to determine the appropriateness of using such data on the basis of Procter & Gamble's desired outcome in each case.

Ivax noted out that the statement which appeared in the BNF had been used in that publication since September 2000 when only two enteric-coated mesalazines were available both of different strengths and clearly not interchangeable. For Procter & Gamble to make use of such wording to support its case today was itself somewhat of an extrapolation. In any event, and more importantly, this statement referred to delivery characteristics and Ivax contended that the use of *in vitro* data was wholly appropriate in measuring delivery characteristics as opposed to clinical equivalence.

In relation to Forbes *et al* Ivax noted that this article was a review of a number of other papers with no original data and merely represented the authors' opinion. Ivax also noted that the authors received an unrestricted educational grant from Procter & Gamble to research this review article.

Ivax did not accept that the claim implied clinical equivalence. The advertisement was aimed primarily at pharmacists who were considering whether it was appropriate to dispense Mesren MR against a generic script for mesalazine.

PANEL RULING

The Panel noted that the 'Dear Customer' letter sent to pharmacists announced the launch of Mesren MR 400mg tablets and compared its delivery system and dissolution profile with the two other oral mesalazine 400g preparations available in the UK: Asacol and Ipocol. A figure showed marked *in vitro* degradation of the coating of Ipocol tablets compared to both Mesren MR and Asacol tablets which each showed no visible disintegration at pH 6.4. A subsequent graph compared the *in vitro* dissolution profiles of Mesren, Asacol and Ipocol at pH 7.2. Asacol and Mesren had very similar dissolution profiles whilst that for Ipocol was quite different. The letter noted that a prescription for 'Mesalazine 400mg tablets' could be filled with Mesren, Asacol or Ipocol and went on to state that if a patient had been receiving Asacol, it did not seem advisable to switch them to Ipocol, considering the significantly different *in vitro* dissolution profiles. The sentence continued by stating that 'Mesren, however, has a virtually identical dissolution profile and an identical qualitative formula to Asacol and can therefore be interchanged with confidence'. This claim also appeared in the advertisement which was headed 'Interchangeability of Oral Mesalazines' and similarly reviewed *in vitro* dissolution data for all three products and considered their interchangeability.

The Panel noted the similarity of the *in vitro* dissolution profiles for Mesren and Asacol. The parties had submitted, however, that *in vitro* dissolution profiles and qualitative formulae were only two factors which might impact on clinical interchangeability. The BNF September 2003 stated that 'The delivery characteristics of enteric-coated mesalazine preparations may vary; these preparations should not be considered interchangeable'. The Panel noted, however, that only two 400mg modified-release preparations were listed in that edition of the BNF, Asacol and Ipocol; Mesren MR had not been launched at that time.

The Panel noted Ivax's submission that the claim at issue was intended to inform a pharmacist that a prescription for mesalazine 400mg modified release could be filled with either Mesren MR or Asacol. In the Panel's view, however, the claim went further than that. The claim regarding the interchangeability of Mesren and Asacol had been immediately preceded, in the same sentence, by a reference to switching patients from Asacol to Ipocol [this did not appear in the same sentence but in the preceding sentence to the claim at issue]. The Panel considered that in the context in which it appeared the claim that Asacol and Mesren 'can therefore be interchanged with confidence' was not limited to a pharmacist's dispensing choices when faced with a generically written prescription from a newly diagnosed patient, it implied that Mesren MR could be given to patients who had previously received Asacol ie the two products were clinically equivalent. There was no clinical data to show that this was so. The Panel considered that the letter and advertisement were misleading in this regard and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled in respect of each item.

APPEAL BY IVAX

Ivax submitted that the Panel had misinterpreted its case in respect of the BNF. The Panel noted that Mesren had not been launched at the time of the September 2003 edition of the BNF which stated 'The delivery characteristics of enteric-coated mesalazine preparations may vary; these preparations should not be considered interchangeable'. This statement was first made in the BNF in September 2000 when there were only two enteric-coated mesalazine products available, both of different strengths and therefore quite obviously not interchangeable. Whilst this warning might have been valid at the time, it was somewhat of an extrapolation for Procter & Gamble to rely on it in support of its case now. Ivax was not merely pointing out that Mesren was not available in September 2003. Furthermore it was clear that *in vitro* dissolution data was an entirely appropriate method of measuring delivery characteristics as opposed to clinical equivalence.

Ivax noted that the Panel was incorrect in its statement that 'The claim regarding the interchangeability of Mesren and Asacol had been immediately preceded, in the same sentence, by a reference to switching patients from Asacol to Ipocol'. These assertions were contained in separate sentences, a fact that fundamentally impacted on the interpretation of the claims and therefore on the conclusions that the Panel had reached based on this mistake.

Ivax noted that the paragraphs of the advertisement at issue, entitled 'Mesalazine prescribing and dispensing', discussed two elements – the prescription of mesalazine followed by its dispensing. The fact that there were two distinct elements would lead the informed reader (to whom the advertisement was aimed) to expect a logical progression from one element to the next, as was the case. The first sentence clearly dealt with prescription. The second sentence addressed the dispensing of mesalazine under a prescription. The paragraph logically continued to address the dispensing element in the final two sentences. Therefore the statement that Asacol and Mesren could be 'interchanged with confidence' was clearly referring to the dispensing of mesalazine and was not an assertion based on clinical equivalence at a prescribing level. It was based, as explained within the advertisement, on the dissolution profiles of the two preparations and was supported by the dissolution results shown in the advertisement.

Ivax submitted that the Panel's ruling was based, in part, on misinterpretation and incorrect facts, which went to the heart of the understanding of the advertisement. The logical progression through the paragraph in question, as suggested by its title, would not lead the qualified professional reader to interpret the statement as one suggesting clinical equivalence between Asacol and Mesren, but instead should simply reinforce the fact that the dissolution profiles of the two preparations were virtually identical, and that in dispensing against a prescription for mesalazine, Asacol and Mesren were interchangeable.

COMMENTS FROM PROCTER & GAMBLE

Procter & Gamble considered that the key issue was whether the claim 'Mesren, however, has a virtually identical dissolution profile and an identical quantitative formula to Asacol and can therefore be interchanged with confidence,' constituted a claim of clinical equivalence. The Panel found that the natural meaning of Ivax's claims was one of clinical equivalence ('ie the two products were clinically equivalent'), and 'There was no clinical data to show that this was so', so that the claims were 'misleading in this regard and could not be substantiated'.

Procter & Gamble noted that Ivax had never disputed that clinical data were required to substantiate claims of clinical equivalence, nor that it had no such data. Ivax's case was that its advertisements were not intended to claim clinical equivalence. Ivax's appeal similarly was only on the Panel's interpretation of the advertisements arguing that the intended meaning was not that of clinical equivalence. It seemed to be accepted that if this was the meaning then there was no data to support it, meaning that the advertisements were in breach of the Code. The grounds of Ivax's appeal appeared to be trivial objections to the way the Panel's ruling was expressed rather than any hard evidence or argumentation to show why it was wrong.

Procter & Gamble submitted that Ivax's point that the statement in the BNF regarding non-interchangeability of mesalazines was first made in September 2000, was a distraction from the main issue. It did not affect the question of whether the claims in the material at issue constituted claims of clinical equivalence. It was clear in reading the Panel's ruling that it knew the reference had been repeated in 2003 and it was clearly given due weight, taking into account Ivax's initial response.

Procter & Gamble noted that Ivax had contended that, 'Furthermore it was clear that *in vitro* dissolution data was an entirely appropriate method of measuring delivery characteristics as opposed to clinical equivalence'. Procter & Gamble alleged that this did not seem to help Ivax's case if the claim was in fact to clinical equivalence. If the *in vitro* data was to be used only to measure delivery characteristics, it could not be used as the basis for the claim, '[Asacol and Mesren] can therefore be interchanged with confidence', which clearly encompassed far more than just delivery characteristics.

Procter & Gamble noted that the Panel stated in its ruling that, 'The claim regarding the interchangeability of Mesren and Asacol had been immediately preceded, in the same sentence, by a reference to switching patients from Asacol to Ipocol'. As Ivax had indicated, the reference and the claim were in separate sentences. These sentences, however, were consecutive, and were evidently linked by the use of the word, 'however':

'If a patient has been receiving Asacol it does not seem advisable to switch them to Ipocol, considering the significantly different *in vitro* dissolution profile. Mesren, however, has a virtually identical… and can therefore be interchanged with confidence'.

Procter & Gamble alleged that despite the fact that the reference to switching and the claim of interchangeability occurred in separate (yet consecutive) sentences, it was clear that both were part of the same message. Whether they were linked by a comma or by use of the conjunction, 'however', had not affected the impression given.

Procter & Gamble's view was that Ivax's statement that this minor error 'fundamentally impacted on the interpretation of the claims and therefore on the conclusions that the Panel had reached based on this mistake' overstated the true position. The Panel had clearly and correctly understood the overall tenor and context of the claim.

Procter & Gamble noted Ivax's argument in its appeal that the paragraph at issue was headed, 'Mesalazine prescribing and dispensing', this heading was only used in the advertisement and not in the letter to pharmacists.

Procter & Gamble considered that Ivax seemed to be trying to state that the claims should be treated differently if related to prescribing or dispensing. The claim of interchangeability was equally misleading to the prescriber or dispenser, implying clinical equivalence despite an absence of clinical data in support. The outcome of importance was the therapy supplied to the patient, rather than the precise details of prescribing or dispensing. Prescribing or dispensing by brand were both tools designed to ensure that each patient was maintained on a constant therapy, unless a specific decision was made by the prescriber to change. Whether the claim that Mesren could be 'interchanged with confidence' related to prescribing or dispensing was irrelevant, and did not alter the fact that this claim clearly implied clinical equivalence.

Procter & Gamble considered that Ivax's appeal showed no compelling reason to overturn the Panel's ruling that the claim to be able to interchange Mesren and Asacol with confidence was one of clinical equivalence between the two. Clinical claims extrapolated from *in vitro* evidence were in breach of Clause 7.2 of the Code. Clause 7.4 was also breached, given that there were insufficient data to substantiate the claims. Neither point seemed to be contested once it was accepted or found that the claim was one of clinical equivalence.

Procter & Gamble submitted that Ivax's argument that the ruling on the point of interpretation should be set aside because the test should be that of the 'qualified professional' reader did not advance its case. The purpose of the Code was to regulate advertising directed to such readers. The Panel was extremely experienced in judging the meaning of advertising to health professionals, and in ruling on its compliance with the Code. The Panel was thus well aware of the context in which the claim was made and brought its experience to bear in making its ruling. In the absence of any compelling reason why the Panel erred in its finding, Procter & Gamble requested that the original ruling of breaches of Clauses 7.2 and 7.4 be upheld.

APPEAL BOARD RULING

The Appeal Board noted that oral mesalazine exerted a topical action within the bowel. Its clinical effect was not dependent upon blood levels but upon the amount of mesalazine which reached the site of inflammation. Although the *in vitro* dissolution profiles of Asacol and Mesren were similar there was no *in vivo* data to show that the two products delivered the same amount of mesalazine to the same site in the bowel. The Appeal Board noted Ivax's submission that it was not claiming that Asacol and Mesren were clinically equivalent.

The Appeal Board noted the two sentences at issue:

'If a patient has been receiving Asacol it does not seem advisable to switch them to Ipocol, considering the significantly different *in vitro* dissolution profiles. Mesren, however, has a virtually identical dissolution profile and an identical qualitative formula to Asacol and can therefore be interchanged with confidence.'

The Appeal Board considered that the two sentences were inextricably linked. The first referred to a patient, a switch in therapy and dissolution profiles. The second sentence continued the discussion of dissolution profiles and stated that Mesren and Asacol could be 'interchanged with confidence'. Given the clinical references in the first sentence the Appeal Board considered that the second would be read in a similar light and 'interchanged' would be interpreted as a therapy switch which could be undertaken 'with confidence'. Readers would assume that Asacol and Mesren were clinically equivalent. There was no data to show that that was so. The Appeal Board thus considered that the letter and the advertisement were misleading in this regard and upheld the Panel's rulings of breaches of Clauses 7.2 and 7.4 of the Code. The appeal was unsuccessful.

Complaint received **15 January 2004**

Case completed **7 May 2004**

CASE AUTH/1549/1/04

GENERAL PRACTITIONER v WYETH

Arrangements for a meeting

A general practitioner complained about a meeting sponsored by Wyeth and run in association with the NHS Alliance. The meeting was to be held from Friday, 2 April, to Sunday, 4 April, in Brussels as part of Wyeth's 'Support in Primary and Specialists Care' initiative. A contract representative had called to tell him about the meeting and on the back of her business card she had written 'I've got an invitation to a meeting in Brussels – could I see you for a minute?'.

The complainant considered that the seminar could have taken place in the UK, and did not add value to the education and training of GPs over and above what was currently being offered to them within the NHS. The complainant thus alleged that the free attendance at the seminar in Brussels, at an estimated cost of £500 per person, constituted a breach of the Code with regard to excessive inducement.

The Panel noted that the Code did not prevent companies from holding meetings for UK health professionals at venues outside the UK, but the supplementary information stated that there had to be valid and cogent reasons for so doing and that the impression created by the arrangements for any meeting must be borne in mind. It should be the programme that attracted delegates, not the associated hospitality or venue.

Wyeth was to pay for UK health professionals to attend a meeting in Brussels. It was immaterial that the meeting was non-promotional. A document entitled 'Summary of Stepping Forward in Primary Care 2003' referred to comparable meetings which would take place in 2004 in London, Manchester and Brussels. The Panel noted from the invitation to the Brussels meeting that 'Stepping Forward in Primary Care' would bring together up to 160 representatives from primary care organizations and other NHS leaders to debate the latest issues and share ideas. GP, pharmacist and nursing accreditation was being sought. Topics to be covered included, *inter alia*, an update on policies of the Department of Health, extended prescribing, unified prescribing and employment law. The whole weekend was thus for UK health professionals to discuss UK medical practice.

The Panel considered that the educational content of the meeting was not unreasonable; it would be of interest to the audience and the balance between education and other activities was not unreasonable. However the Panel was concerned about the choice of venue and considered that delegates would be attracted by that rather than the programme. The Panel noted Wyeth's reasons for choosing Brussels but did not consider that these were sufficient to justify holding a meeting for UK health professionals outside the UK. Two other meetings in the series were to be held in the UK.

Whilst reasonable hospitality could be provided the cost of a meeting should not exceed that which participants might normally pay for themselves. GP, pharmacist and nursing accreditation for the meeting was being sought and attendees would thus be a mixture of doctors, pharmacists and nurses. The average cost per head was expected to be £523. The Panel considered that for some of the delegates this would exceed that which they would normally pay for themselves.

The Panel considered that the arrangements for the meeting were unacceptable. A breach of the Code was ruled. The Panel considered that high standards had not been maintained and a further breach was ruled. These rulings were appealed.

The Appeal Board noted that meetings organised by pharmaceutical companies which involved UK health professionals at venues outside the UK were not necessarily unacceptable. There had, however, to be valid and cogent reasons for holding meetings at such venues. The Appeal Board noted that each had to be judged on its own particular merits. In respect of the meeting at issue the Appeal Board noted that it was one of a series of five similar events. Of the five meetings three were to be in Brussels, one in London and one in Manchester. The Appeal Board noted that the meeting agenda was educational with an emphasis on NHS policy issues and its content had not been criticised. In the Appeal Board's view the hotel accommodation provided for the meeting in Brussels, whilst of a reasonable business standard, could not be considered extravagant; delegates would be attracted by the educational content rather than the location. Brussels had excellent travel links and the cost of travelling there was comparable with the cost of travel within the UK. In the Appeal Board's view Brussels would not be considered an exotic location. The Appeal Board did not consider that the cost was generally more than delegates would pay if they were paying for themselves.

The Appeal Board considered that, on balance, for the reasons listed above, the arrangements for the meeting were not unacceptable. The Appeal Board did not consider that high standards had not been maintained. No breaches of the Code were ruled in relation to the meeting.

The representative had written on the back of her business card 'I've got an invitation to a meeting in Brussels – could I see you for a minute?'. The Panel noted Wyeth's submission that the representative had been asked by the receptionist to describe the meeting in a brief note on the back of her business card. The first priority for representatives must be to ensure that their activities complied with the Code regardless of their customers' wishes. The note on her business card gave the impression that she was using the invitation to the meeting as a way of gaining an interview with the complainant either immediately or some time in the future. The Panel considered that by writing such a message the representative had sought to use an inducement to gain an interview. A breach of the Code was ruled which was accepted by Wyeth. The Panel

considered that the representative had failed to maintain a high standard of ethical conduct in the discharge of her duties and to comply with all relevant provisions of the Code. A further breach was ruled which was appealed.

With regard to the conduct of the representative, the Appeal Board considered that she had failed to maintain a high standard of ethical conduct in the discharge of her duties and had not complied with all the relevant provisions of the Code. The Panel's ruling of a breach of the Code was upheld.

A general practitioner complained about a meeting sponsored by Wyeth Pharmaceuticals and run in association with the NHS Alliance. A letter of invitation stated that the meeting, to be held from Friday, 2 April, to Sunday, 4 April 2004, in Brussels was part of Wyeth's 'Support in Primary and Specialists Care' initiative. A contract representative had called to see the complainant to tell him about the meeting; on the back of her business card she had written 'I've got an invitation to a meeting in Brussels – could I see you for a minute?'.

COMPLAINT

The complainant noted that the meeting would last a whole weekend and largely deal with issues that were integral to current NHS primary care policy. A large number of the speakers were from the Department of Health who were obviously paid out of the profits Wyeth made from medicine sales, including those to the NHS.

The complainant considered that the seminar could have taken place in the UK, and did not add value to the education and training of GPs over and above what was currently being offered to them within the NHS. The complainant thus alleged that the free attendance at the seminar in Brussels, at an estimated cost of £500 per person, constituted a breach of the Code of Practice with regard to excessive inducement.

The complainant supplied a copy of a letter, the programme and the card left for him by the representative, which he submitted made it clear that the offer of a free place was also being used to gain access.

When writing to Wyeth the Authority asked it to respond in relation to Clauses 9.1, 15.2, 15.3, 19.1 and 2 of the Code.

RESPONSE

Wyeth explained that it provided an educational grant to the NHS Alliance to support the 'Stepping Forward in Primary Care' meetings. The NHS Alliance was an independent, well-known membership body for primary care organisations in the UK and individuals who worked in primary care, and provided an important function in the development and dissemination of best practice within the NHS. It was wholly independent from Wyeth and the pharmaceutical industry and was not a commercial organisation.

The NHS Alliance had worked with Wyeth for the last three years in presenting the 'Stepping Forward in Primary Care' meetings. These had been attended by many hundreds of doctors, pharmacists, nurses, managers and appropriate administrative staff. This was the first complaint Wyeth had received. Although Wyeth put the programme and other meeting details through its internal approval process (as required by the Code), the programme was jointly developed and agreed by Wyeth and the NHS Alliance. Wyeth met the cost of the meetings.

The meetings were entirely non-promotional; the NHS Alliance would have refused to be associated with Wyeth were this not the case. No product-related materials were used or presented in the meetings, and Wyeth did not have a promotional stand at the meetings. The focus of the meetings was the local implementation of national policy such as national service frameworks, performance management and other important issues as set out in the programme agenda, and the meetings were believed by the NHS Alliance to be of considerable value to the NHS. Wyeth benefited from the kudos and reputational benefits of sponsoring the meetings, together with the opportunity to build relationships with its customers. Far from bringing discredit upon, or reducing confidence in, the pharmaceutical industry, the company considered that by supporting meetings of this kind, Wyeth was leading the way in enhancing the pharmaceutical industry's reputation amongst health professionals, as had been demonstrated in independent surveys.

Wyeth stated that the NHS Alliance believed that the need for training and discussion about policy implementations had never been greater. Whilst some areas of the NHS made provision for such events, this was by no means uniform and the NHS Alliance considered that there were insufficient opportunities provided by the NHS for this type of meeting. Wyeth did not agree with the complainant's comment that the meetings added nothing to what was already provided by the NHS.

Feedback collected about the meetings had been very positive, and there was a significant level of repeat attendance and contribution.

Although the Code provided that accreditation did not mean that arrangements were automatically acceptable under the Code, the 'Stepping Forward in Primary Care' meetings were accredited for PGEA points by the UK National Accreditation Panel.

Speakers were of a high calibre, and had included the NHS National Clinical Director of Primary Care, the Chair of the NHS Alliance and nationally respected figures from independent organisations and those in frontline clinical practice. Wyeth did not consider such high profile individuals would align themselves to events that they perceived to be promotional.

Over the three years that the 'Stepping Forward in Primary Care' meetings had been running, the programme and structure had been fine-tuned and optimized according to speaker and delegate feedback. Currently, delegates arrived on the Friday night with registration from 18.15 onwards. Following a Chairman's welcome, there was a lecture, which was followed at 20.30 by a dinner in the hotel. Arriving on the Friday night enabled an early start on

the Saturday, with delegate registration from 08.00 (delegates were required to register before each of the four educational sessions to ensure attendance and to get their PGEA points). A series of lectures and workshops followed, including buffet lunch at 13.15 to 14.15, and the meeting ended for the day at 15.30 – a total meeting duration of 5.5 hours for the day. A standard business grade dinner was provided at an external restaurant in the evening.

On the Sunday morning, delegate registration took place from 08.30, with lectures from 09.30 to 12.30. An optional buffet lunch was then provided and delegates left immediately to travel back to the UK. Wyeth considered that the meeting programme comprised a substantial and adequate amount of educational content which justified two nights' accommodation. Wyeth provided copies of the meeting documentation which gave details of the programme, speakers and workshop facilitators.

Wyeth also provided a copy of the briefing document which was given to Wyeth attendees for the comparable meeting held in 2003. Wyeth noted that the role of Wyeth delegates was not promotional and was geared to ensuring the meeting ran smoothly. It was clearly stated that delegates 'will be attending all meals/dinners provided' and that 'you do not have the provision to make other [i.e. additional] arrangements'. It was further stated: 'Please remember all hospitality/activity should be within ABPI guidelines'. This written guidance to Wyeth attendees was in addition to verbal briefings at the meeting itself.

Wyeth considered that the costs of the meetings (£523 per person) were reasonable and were no higher than that which delegates would normally pay if paying for themselves. The hospitality provided was clearly secondary to the main purpose of the meeting – education. Wyeth provided a breakdown of the costs of the meetings.

Wyeth submitted that a major reason for choosing Brussels was to ensure the venue was maximally conducive to learning and would avoid distractions. From previous experience, the NHS Alliance and Wyeth had found that meetings in Brussels had better attendance rates at educational sessions than similar events in London where there was a higher degree of delegate absenteeism for individual sessions. This was presumably because 'captive' delegates in Brussels did not have their own transport and could not so easily leave the meeting compared with London. Sessions were also less likely to be interrupted by bleeps and mobile phone calls in Brussels than in London. These were important, genuine considerations for the organisers to maximise the impact of educational meetings.

Brussels was a major transport hub in close proximity to the UK, and was quicker and easier to travel to from many UK locations than for intra-UK travel. Brussels offered the additional advantage over most European cities of Eurostar connections as well as flights. Brussels would not be considered by most people an 'exotic' location, and indeed was chosen over Paris to ensure this was the case. It was also in northern Europe with its associated weather, so by definition was unlikely to be perceived as a holiday location. Most importantly, however, as the centre for the European Commission and many other European organisations, Brussels had a large number of hotels and conference centres.

The meeting venue chosen in Brussels was a middle range, business style hotel. No associated activities or outings were organised for delegates that might be perceived as a 'jolly', and lunches were buffet-style in the hotel and not at an expensive restaurant. The restaurant dinner on the Saturday evening was also mid-range, costing about the same as the hotel dinner. Overall, Wyeth considered that it was clearly the programme and not the venue or associated hospitality that would attract delegates to the meeting, as confirmed by feedback forms completed by the delegates.

Wyeth stated that the sales representative who had called upon the complainant was highly experienced, and had passed the ABPI representative's examination. She was reported by her manager to be mature, level-headed, honest and reliable.

As the complainant was a senior figure in the local primary care trust, Wyeth believed that the 'Stepping Forward in Primary Care' meeting would be highly relevant and hence of interest, as part of the very specific audience to whom the meeting was targeted.

Wyeth decided that it was important for the invitations to be made personally so that the educational focus of the meeting could be explained and any further information given. Where such invitations were sent in the mail, most of them were treated as promotional material and routinely thrown away. Furthermore, the company needed to have a response as soon as possible so that it could invite additional delegates in place of any who declined.

It was the representative's responsibility to make the invitation on behalf of Wyeth. When she went to the surgery, she was told by the receptionist that the complainant never saw company representatives, and so left her business card with the note 'I've got an invitation to a meeting in Brussels – could I see you for a minute?' on the back, together with the invitation and full meeting details, including the programme. She did not see the complainant in person, but left it to him to contact her if he was interested in the meeting. As the purpose of the representative's visit had already been clearly established with the receptionist, the words she wrote on the card did not amount to an inducement or subterfuge to gain an interview.

It was difficult to envisage how the representative could have adequately described the objectives and nature of the 'Stepping forward' meeting in a brief note on the back of a business card – she was specifically requested by the receptionist to do so, and hence was put in a difficult position. The card message was not an inducement to gain an interview, as it was supplied on specific request, and was supplied in addition to full meeting details to ensure there was no misunderstanding as to the purpose of the interview. Specifically, it would be clear from the programme and meeting details that the meeting was educational, and that it was the programme and not

the venue that would be of interest to delegates. Wyeth thus considered that it would be inaccurate and unfair to judge the business card note in isolation and out of context, and it denied breaches of Clauses 15.2 or 15.3.

Wyeth noted that the supplementary information to Clause 19.1 stated that in determining whether a meeting outside the UK was acceptable or not, 'as with meetings held in the UK…..consideration must also be given to the educational programme, overall cost, facilities offered by the venue, nature of the audience, hospitality provided and the like. As with any meeting it should be the programme that attracts delegates and not the associated hospitality or venue'. Whether or not the meeting took place in the UK, all the provisions of the Code had to be considered.

Wyeth considered that it had shown that in matters such as the educational programme, overall cost, facilities offered by the venue, nature of the audience and hospitality provided for this meeting, the company had complied with the Code. The importance and educational value of the meeting to senior members of the NHS, including GPs, had been demonstrated.

If in all other respects except its location a meeting complied with the requirements of the Code, Wyeth did not consider that a meeting in Brussels should be considered unacceptable simply because it was outside the UK, or that such a meeting in, for example, Edinburgh or London would be considered automatically acceptable simply because it was within the UK.

So far as using Brussels as a venue was concerned, the overall cost was reasonable, Brussels was highly convenient from a travel point of view, the company achieved a higher level of attendance in Brussels due to fewer distractions and there was no level of hospitality associated with the intrinsic attraction of Brussels which would make Brussels a more attractive venue to delegates simply because of its location. Wyeth noted that it was aware of its responsibilities to the industry in this area and its guidelines for meetings, including the provisions for meetings outside the UK, took into account past rulings, in particular Cases AUTH/626/10/97, AUTH/627/10/97 and AUTH/1191/6/01, as well as the specific details of the Code itself. Wyeth noted from these cases that, provided certain conditions were met, it was considered acceptable for meetings to be held outside the UK.

Wyeth was proud of its 'Stepping Forward in Primary Care' series of meetings and was very happy for the arrangements to be generally known. The company considered that the overall impression of the meeting arrangements was of a very high standard of topical, needed and welcome education which was closely focused on its intended audience and which did not promote any of the sponsor's products.

Wyeth further considered that Brussels as a venue was no more attractive than a number of alternative locations in the UK, such as Edinburgh or London, and that it would not be justifiable to conclude that Brussels was unacceptable on the sole ground that it was outside the UK. The company considered that it was the educational programme that attracted its delegates to this meeting and not any associated hospitality or the venue and that, taking all factors into account, the meeting complied with the Code and was not in breach of Clause 19.1.

Wyeth considered that it had shown that it and the representative maintained high standards at all times and that, in sponsoring a valuable and educational meeting for primary care health professionals, it had not done anything to bring discredit upon, or reduce confidence in, the pharmaceutical industry. The company thus denied any breaches of Clauses 9.1 or 2.

PANEL RULING

The Panel noted that Clause 19.1 of the Code permitted companies to provide appropriate hospitality to members of the health professions and appropriate administrative staff in association with scientific and promotional meetings, scientific congresses and other such meetings. Hospitality must be secondary to the purpose of the meeting and the level of hospitality offered must be appropriate and not out of proportion to the occasion. The supplementary information to Clause 19.1 explained that the provision of hospitality included payment of reasonable, actual travel costs which a company might provide to sponsor a delegate to attend a meeting.

The Panel noted that the Code did not prevent companies from holding meetings for UK health professionals at venues outside the UK but the supplementary information to Clause 19.1 stated that there had to be valid and cogent reasons for so doing. The supplementary information to Clause 19.1 also stated that the impression created by the arrangements for any meeting must be borne in mind. It should be the programme that attracted delegates, not the associated hospitality or venue.

The Panel noted that Wyeth was to pay for UK health professionals to attend a meeting in Brussels. It was immaterial that the meeting was non-promotional; Clause 19 of the Code applied equally to promotional meetings and non-promotional meetings. A document supplied by Wyeth entitled 'Summary of Stepping Forward in Primary Care 2003' referred to the comparable meetings which would take place in 2004 in London, Manchester and Brussels. The Panel noted from the invitation to the Brussels meeting that 'Stepping Forward in Primary Care', would bring together up to 160 representatives from primary care organizations and other NHS leaders to debate the latest issues and share ideas. GP, pharmacist and nursing accreditation was being sought. Topics to be covered included, *inter alia*, an update on policies of the Department of Health, extended prescribing, unified prescribing and employment law. The whole weekend was thus for UK health professionals to discuss UK medical practice.

The Panel considered that the educational content of the meeting was not unreasonable; it would be of interest to the audience and the balance between education and other activities was not unreasonable. However the Panel was concerned about the choice of venue and considered that delegates would be

attracted by that rather than the programme. The Panel noted Wyeth's reasons for choosing Brussels but did not consider that these were sufficient to justify holding a meeting for UK health professionals outside the UK. Two other meetings in the series were to be held in the UK.

The Panel noted that whilst reasonable hospitality could be provided the cost of the meeting should not exceed that which participants might normally pay for themselves. The Panel considered that as GP, pharmacist and nursing accreditation for the meeting was being sought, attendees would be a mixture of doctors, pharmacists and nurses. The average cost per head was expected to be £523. The Panel considered that for some of the delegates this would exceed that which they would normally pay for themselves.

The Panel considered that the arrangements for the meeting were unacceptable. A breach of Clause 19.1 was ruled. The Panel further considered that high standards had not been maintained. A breach of Clause 9.1 was ruled. These rulings were appealed by Wyeth.

The Panel noted that a ruling of a breach of Clause 2 was a sign of particular censure and reserved for such use. The Panel did not consider that the arrangements for the meeting were such as to warrant such a ruling.

With regard to the representative the Panel noted that on the back of her business card she had written 'I've got an invitation to a meeting in Brussels – could I see you for a minute?'. The Panel noted Wyeth's submission that the representative had been asked by the receptionist to describe the meeting in a brief note on the back of her business card. The first priority for representatives must be to ensure that their activities complied with the Code regardless of their customers' wishes. Wyeth had not described everything that had happened when the representative had visited the complainant's surgery. The Panel did not know whether, having written on her business card and submitted it and the other documents, the representative left straight away or waited to see if the complainant would see her. It was immaterial that in the end the representative had failed to see the complainant. The note on her business card gave the impression that she was using the invitation to the meeting as a way of gaining an interview with the complainant either immediately or some time in the future. The Panel considered that by writing such a message the representative had sought to use an inducement to gain an interview. A breach of Clause 15.3 was ruled. This ruling was accepted by Wyeth. The Panel further considered that the representative had failed to maintain a high standard of ethical conduct in the discharge of her duties and to comply with all relevant provisions of the Code as required under Clause 15.2. A breach of that clause was also ruled. This ruling was appealed by Wyeth.

APPEAL BY WYETH

Wyeth submitted that the meeting was wholly educational with no promotional activity and no Wyeth stand. The company noted that it had received highly favourable delegate feedback about previous 'Stepping Forward in Primary Care' meetings. From the delegates' perspective, it was clearly the programme that attracted them and not the associated hospitality or venue.

Wyeth did not accept the Panel's view that it was 'immaterial' that the meeting was non-promotional. Although Clause 19 applied equally to promotional and non-promotional meetings, the non-promotional nature, content and objectives of this programme directed at much-needed and highly-appreciated training for NHS professionals was, in Wyeth's view, clearly relevant to alleged breaches of Clauses 9.1 and 15.2. Wyeth submitted that even in relation to Clause 19.1, the non-promotional nature of the meeting (comprehensively endorsed by attendees and participants) as stated in its initial response was a very important factor in delegates' decisions to attend, and was therefore significant in deciding whether it was the programme that attracted them rather than the hospitality or venue.

Wyeth noted that the supplementary information to Clause 19.1 stated that, as with meetings held in the UK, consideration had to be given to the educational programme, overall cost, facilities offered by the venue, nature of the audience, hospitality provided and the like, and that it should be the programme that attracted delegates and not the associated hospitality or venue. Wyeth submitted that, with the exception of venue and cost, the Panel had concluded that the company had complied with all of these requirements.

Wyeth submitted that in selecting Brussels as one of the locations for its 'Stepping Forward in Primary Care' meetings, it had carefully considered Clause 19.1 together with previous Panel rulings as well as its own internal policies and guidelines. There was no intention to deliberately choose an exotic location, and indeed a number of otherwise suitable locations such as Paris and Amsterdam were ruled out for this reason. The fact that several 'Stepping Forward in Primary Care' meetings had been held in London and Manchester supported the point that Wyeth was not looking for a venue outside the UK to attract delegates.

Wyeth submitted that as with all such meetings, it was necessary to choose a major European city in order to have adequate transport links and availability of conference facilities. This had left a relatively small list of potential cities, of which Brussels was a top choice because of its excellent transport links, reasonable costs and Wyeth's experience of significantly less session absenteeism in Brussels. It was not considered that delegates would be attracted by Brussels as a venue rather than the programme. These factors all contributed to the choice of Brussels as a venue.

Wyeth submitted that as described in its response to the complaint, hospitality comprised business-grade meals, with no extras such as tours. The absence of non-educational activities was clearly apparent from the meeting programme.

In summary, Wyeth submitted that it had made every effort to select an appropriate venue, and that Brussels was an acceptable venue. It was the educational, non-

promotional programme that attracted delegates, and not the associated hospitality or venue, as confirmed in feedback received from delegates.

Wyeth noted that, as the Panel had not given any reasons for its conclusion that delegates would be attracted by the Brussels venue rather than the programme, it had been unable to deal with the reasons specifically. For the reasons set out here and in the response to the original complaint, no grounds had been established for concluding that it was the attraction of Brussels *per se* that attracted delegates rather than the programme.

Wyeth submitted that the cost of the Brussels meeting was reasonable, not excessive, and was comparable if not lower than holding a similar meeting in the UK. There were many examples of comparable training meetings for NHS staff, held in the UK, costing a similar or greater sum than £523 per head. Moreover, these meetings usually excluded the costs of accommodation, travel and meals. Some specific examples were provided.

Wyeth disagreed with the Panel's view that the cost of the meeting exceeded that which participants would normally pay for themselves. Whilst it would be possible to secure cheaper accommodation and food, but not always possible to do so, such venues would not usually be able to host a conference. In order to make a fair comparison, it would be necessary to look at the cost of a comparable conference-style hotel. Wyeth noted that the 'European Code of Practice for the Promotion of Medicines' stated in Article 6 (Gifts and hospitality) that the cost of events 'must not exceed what recipients would normally be prepared to pay for themselves *in the same circumstances*'.

Given that Wyeth obtained bulk discounts, it further contended that delegates would probably be unable to obtain rooms at conference-style hotels at a lower cost than it had. Moreover, flights were booked at economy rates so it would be similar to what a delegate would pay themselves.

Wyeth did not agree with the Panel's statement that the cost per head *for some of the delegates* would exceed that which they would normally pay for themselves. Although the Panel had not made this clear, Wyeth assumed that this part of the decision referred to the small percentage of nurses (and possibly pharmacists) whose personal income would not support this level of individual expenditure. All delegates who attended the 'Stepping Forward in Primary Care' meetings did so because it was relevant to their NHS roles and responsibilities and also because this very relevant course contributed to their continuing professional education.

Wyeth submitted that the Panel's ruling based as it appeared on the ability of some delegates to pay personally was therefore flawed as it related to a small percentage of delegates rather than the delegates as a whole and, even then, the Panel had not shown that such delegates would not have been able to have the costs of a comparable course paid on their behalf by their employers.

Wyeth submitted that its arrangements relating to the venue and related costs were not unacceptable in respect of the choice of Brussels and in relation to the overall level of costs, and consequently it requested a ruling of no breach of Clause 19.1. So far as Clause 9.1 was concerned, the Panel had not given any reasons for ruling a breach and, even if the Appeal Board considered Clause 19.1 to have been breached, Wyeth did not consider that a breach of Clause 9.1 must automatically follow. Wyeth submitted that at all times it had maintained high standards, as was confirmed by the delegate feedback included in its original response. Moreover, in the three years that the 'Stepping Forward in Primary Care' meetings had been running, only the current complaint had been received.

Wyeth submitted that a distinction between promotional and non-promotional meetings was, contrary to the Panel's view, an important aspect to this case in relation to alleged breaches of Clauses 9.1 and 15.2. Wyeth submitted that it had shown that it had taken very seriously its responsibilities for maintaining high standards at all times and that the facts would not support a finding that it had breached Clauses 9.1 or 15.2.

With regard to the activities of the representative Wyeth stated that the primary purpose of the interview she tried to organise with the doctor was to discuss an educational meeting and obtain his response. Wyeth noted that it had not described everything that had happened at the representative's visit and it was unaware whether the complainant had provided full details to the Panel, it added that the complainant had telephoned the representative later that afternoon and the meeting was discussed. Wyeth provided a full description of the representative's visit to the surgery and conversation with the complainant. This was reproduced from a report by the representative's manager.

Wyeth submitted that although the representative might have made a mistake in what she wrote on the card, there was nothing intrinsically wrong in wanting to leave the invitation and obtain a response, and that the representative's actions on that day had not, therefore, merited the further sanction of a breach of Clause 15.2.

COMMENTS FROM THE COMPLAINANT

The complainant noted that Wyeth had stated that its representative had only wished to discuss the educational meeting in question. The complainant alleged that this was not provable. The letter of invitation had not required further explanation. The use of a calling card and the request for a personal meeting was unnecessary. It suggested that Wyeth had chosen to deliver the invitations personally to achieve a greater interpersonal effect, its purpose would be to obligate individuals to be supportive of its future aims. This was damaging to Wyeth's competitors and threatened to raise overall expenditure on similar activities by all companies thus raising costs within the industry and for the NHS.

The complainant alleged that Wyeth could have distributed the invitation in a different way such as to avoid his complaint altogether. The complainant

suggested that the NHS Alliance could have mailed the invitation from the chairman. It could have sent an invitation to the primary care trust for use with the most appropriate individual within the organisation. Thus the primary care trust could have decided as an organisation whether there was an educational need or not. Neither approach could have been construed as Wyeth trying to influence individuals.

The complainant noted that Wyeth had portrayed him and his practice as hostile to company representatives. This was not so. Examples were provided. The complainant was concerned with the overall impact of Wyeth's strategy on costs and other companies' behaviour in the NHS.

The complainant noted that Wyeth had stated that the cost of the meeting had not exceeded that which participants would normally pay themselves. The complainant alleged that this was open to considerable doubt, he had personally never paid £523 to attend an educational meeting of this nature, and in 18 years in the NHS he had not met another GP paying this much money for this type of event out of their own pocket. Similar content as offered at the meeting would be readily accessible for the target audience through web based resources, attendance at primary care trust meetings, local and regional meetings.

APPEAL BOARD RULING

The Appeal Board was concerned that, in its submission, Wyeth had unfairly compared the costs of its meeting with other meetings organised for similar audiences. Like had not been compared with like.

The Appeal Board noted that the supplementary information to Clause 19.1 of the Code stated that meetings organised by pharmaceutical companies which involved UK health professionals at venues outside the UK were not necessarily unacceptable. There had, however, to be valid and cogent reasons for holding meetings at such venues. The Appeal Board noted that each had to be judged on its own particular merits. In respect of the meeting at issue the Appeal Board noted that it was one of a series of five similar events. Of the five meetings three were to be in Brussels, one in London and one in Manchester. The Appeal Board noted that the meeting agenda was educational with an emphasis on NHS policy issues and its content had not been criticised. In the Appeal Board's view the hotel accommodation provided for the meeting in Brussels, whilst of a reasonable business standard, could not be considered extravagant; delegates would be attracted by the educational content rather than the location. Brussels had excellent travel links and the cost of travelling there was comparable with the cost of travel within the UK. In the Appeal Board's view Brussels would not be considered an exotic location. The Appeal Board did not consider that the cost was generally more than delegates would pay if they were paying for themselves.

The Appeal Board considered that, on balance, for the reasons listed above, the arrangements for the meeting were not unacceptable. The Appeal Board ruled no breach of Clause 19.1. The appeal on this point was successful. The Appeal Board did not consider that high standards had not been maintained and thus ruled no breach of Clause 9.1. The appeal on this point was successful.

With regard to the conduct of the representative, the Appeal Board considered that she had failed to maintain a high standard of ethical conduct in the discharge of her duties and had not complied with all the relevant provisions of the Code. The Panel's ruling of a breach of Clause 15.2 of the Code was upheld. The appeal on this point was unsuccessful.

Complaint received **22 January 2004**

Case completed **2 June 2004**

GENERAL PRACTITIONER v SCHERING HEALTH CARE

Promotion of Levonelle-2

A general practitioner complained about the promotion of Levonelle-2 (levonorgestrel), an emergency contraceptive marketed by Schering Health Care. The complainant alleged that the statement 'Levonelle-2 is not effective once the process of implantation has begun' was not substantiated by the evidence.

The complainant stated that if after ingestion of Levonelle-2, the blastocyst touched the endometrial cells and signalling failure occurred, or even if a single molecular bond already formed between a blastocyst cell and an endometrial cell was broken, or if the early stages of invasion were interrupted as a result, then Levonelle-2 would have an effect once the process of implantation had begun and by current definition miscarriage would occur.

The process of implantation began at a submicroscopic molecular level and it was not possible to directly view this process *in vivo*. Therefore as the researchers were physically and ethically unable to view these early stages of the process of implantation directly *in vivo* in a human subject as the blood and tissue levels of Levonelle-2 were rising, Schering Health Care was unable to make an absolute statement that 'Levonelle-2 is not effective once the process of implantation has begun'.

In the complainant's view Levonelle-2 might be effective once the process of implantation had begun and the statement at issue remained unqualified. Furthermore researchers admitted that they did not know how Levonelle-2 worked and that further investigation was required.

The Panel noted that Section 5.1 of the Levonelle-2 summary of product characteristics (SPC) stated that its precise mode of action was unknown. The SPC stated that it was thought to work mainly by preventing ovulation and fertilization if intercourse had taken place in the preovulatory phase, when the likelihood of fertilization was the highest. It might also cause endometrial changes that discouraged implantation. It was not effective once the process of implantation had begun.

The Panel considered the data provided did not support a role for Levonelle-2 once implantation had occurred. The WHO Task Force on Postovulatory Methods of Fertility Regulation found that efficacy was significantly and inversely related to time since intercourse. Ho and Kwan (1993) found that pregnancy rates in patients who took the medicine within 24 hours were lower than those in patients who took it later. However, the study authors stated that probably because of the small patient numbers the difference was not statistically significant.

Croxatto *et al* (2001) reviewed research to understand how emergency contraception methods acted. Various studies were discussed; Moggia *et al* (1974) proposed that the contraceptive effect was due to changes in the endometrium that prevented implantation. Similar comments were made in relation to Wang *et al* (1998) wherein in relation to the endometrium, preovulatory administration factors believed to be critical for implantation were changed in ways likely to alter endometrial receptivity. When appraising the possible modes of action Croxatto *et al* noted the inverse relationship between the intercourse-treatment interval and efficacy and stated that this lent support to a significant role of pre-fertilization mechanisms in its contraceptive effectiveness.

Durand *et al* (2001) assessed the mechanism of action of levonorgestrel stating that all emergency contraceptive medicines methods in use acted before implantation. The study did not support an anti-implantation contraceptive effect. Marions *et al* (2002) reported that their data suggested that the ovulation process was the main target for emergency contraception with levonorgestrel.

The Panel noted Schering Health Care's comments regarding the use of progesterone or progestogens for the treatment of threatened miscarriage. The Panel also noted, however, that the British National Formulary, September 2003, stated that there was no evidence of benefit and that progestogens were not recommended for such use.

The Panel noted the statement in the Levonelle-2 SPC that the precise mechanism of action was unknown. This was reflected in the additional data provided.

In relation to a leaflet, 'A Health Professional's Guide to Emergency Contraception', the claim 'It is not effective once the process of implantation has begun' appeared within a section entitled 'How does it work'. The claim was taken from the Levonelle-2 SPC. The preceding paragraph in the leaflet described in general terms the mechanism of action of emergency contraception stating that 'The precise mode of action is unknown, however emergency hormonal contraception is thought to work mainly by delaying or preventing ovulation and fertilization …. It may also cause endometrial changes that discourage implantation'. This was referenced to the Levonelle SPC.

The Panel noted the complainant's comments about the implantation process but considered that, given the statement in the SPC and the additional data provided, the statement in the leaflet was not unacceptable. No breaches of the Code were ruled.

Upon appeal by the complainant the Appeal Board noted that in Nygren and Johansson (1975) certain synthetic gestagens had been given orally during 25 early, human pregnancies. The abstract stated that two women aborted after the treatment but judging from the hormonal levels these pregnancies were abnormal and would probably have aborted regardless of the treatment. The complainant pointed out that Nygren and Johansson reported that necrosis was found microscopically near chorionic invasive cells.

The Appeal Board noted that the mechanism of action of Levonelle was incompletely understood. Studies in humans to obtain direct evidence on the

process would not be ethical. Schering Health Care referred to the data showing the inverse relationship between efficacy and length of time from intercourse ie that pregnancy rates increased with time and submitted that this was a strong indication of the prefertilization mode of action and did not support the existence of the mechanism of any action after fertilization. The Appeal Board also noted Section 5.1 of the Levonelle-2 SPC.

The Appeal Board noted that the statement 'It is not effective once the process of implantation has begun' appeared within a section entitled 'How does it work' of the leaflet in question.

The Appeal Board considered that the context of the statement was an important factor. It was included in a detailed guide for health professionals and the relevant section gave full information consistent with the Levonelle-2 SPC about what was known about the mechanism of action.

On balance the Appeal Board considered that, given the SPC, the additional data provided and its context, the statement at issue was not unacceptable. No breaches of the Code were ruled.

A general practitioner complained about the promotion of Levonelle-2 (levonorgestrel), an emergency contraceptive marketed by Schering Health Care Ltd. The complainant had originally complained that there was no evidence to support the statement 'Levonelle-2 is not effective once the process of implantation has begun' which appeared in Section 5.1, Pharmacodynamic properties, of the Levonelle-2 summary of product characteristics (SPC) (Case AUTH/1443/3/03). Having considered Schering Health Care's comments on the matter the Director decided that there was no *prima facie* case for the company to answer because SPCs were excluded from the application of the Code by virtue of Clause 1.2. However the Director decided that the use of the statement at issue, and closely similar statements, in promotional material should be taken up as a fresh complaint (Case AUTH/1464/5/03) wherein the Panel subsequently ruled no breach of the Code.

The complainant subsequently made the present complaint (Case AUTH/1556/2/04) alleging that the statement 'Levonelle-2 is not effective once the process of implantation has begun' was not substantiated by the evidence submitted in Case AUTH/1464/5/03. Paragraph 5.1 of the Constitution and Procedure provided that the Director should normally allow complaints similar to those which had been the subject of a previous adjudication to proceed if, *inter alia*, they were not the subject of appeal to the Code of Practice Appeal Board.

COMPLAINT

The complainant noted that the process of implantation began when the blastocyst touched the endometrium and signalled to the endometrial cells to initiate adhesion; this occurred at a molecular level through extracellular cell adhesion proteins and was followed by blastocyst invasion.

After Levonelle-2 had been ingested the blood and tissue levels steadily rose to their peak. It had been shown to produce adverse endometrial changes and even decidual necrosis. Therefore if the process of blastocyst implantation has just begun as the tissue levels were rising, it might indeed affect the process of implantation: it might cause signalling failure, it might cause extracellular cell adhesion protein bonds to be broken between blastocyst and endometrial cells, it might even cause a newly invasive blastocyst to be rejected.

If after ingestion of Levonelle-2, the blastocyst touched the endometrial cells and signalling failure occurred, or even if a single molecular bond already formed between a blastocyst cell and an endometrial cell was broken, or if the early stages of invasion were interrupted as a result, then Levonelle-2 would definitely have an effect once the process of implantation had begun and by current definition miscarriage would occur.

The process of implantation began at a submicroscopic molecular level and it was not possible to directly view this process *in vivo*. Therefore as the researchers were physically and ethically unable to view these early stages of the process of implantation directly *in vivo* in a human subject as the blood and tissue levels of Levonelle-2 were rising, Schering Health Care was unable to make an absolute statement that 'Levonelle-2 is not effective once the process of implantation has begun'.

Clearly Levonelle-2 might be effective once the process of implantation had begun and the statement at issue remained unqualified. Furthermore the researchers admitted that they did not know how Levonelle-2 worked and that 'further investigation for the contraceptive effects of levonorgestrel' was required.

When writing to Schering Health Care the Authority asked it to respond in relation to Clauses 7.2 and 7.4 of the Code.

RESPONSE

Schering Health Care submitted that the information provided in the leaflet, 'A Health Professional's Guide to Emergency Hormonal Contraception', that Levonelle-2, 'is not effective once the process of implantation has begun', was to be substantiated by the SPC. The company considered it thus fulfilled the requirements of Clauses 7.2 and 7.4 of the Code.

As also stated in the SPC and other materials, the mechanisms of action of Levonelle-2 were not fully understood, although it was recognised that its actions depended upon the stage of the menstrual cycle at application. Support for the SPC statement at issue came in part from the World Health Organisation (WHO) publication on Postovulatory Methods of Fertility Regulation which showed that Levonelle exhibited an inverse relationship between efficacy and the length of time from intercourse to treatment, namely that pregnancy rates increased with time. If Levonelle acted in any way to disrupt an implanted zygote, the efficacy would be maintained or even increased with increased time between intercourse and treatment. Ho and Kwan (1993) found the same trend. This was a strong indication of

the pre-fertilisation mode of action of Levonelle and did not support the existence of the mechanism of any action after fertilisation.

Further indirect evidence, which indicated that Levonelle worked prior to fertilisation (and thus implantation), could be found in the literature. Croxatto *et al* (2001) reviewed the mode of action of levonorgestrel emergency contraception and found that the administration of levonorgestrel during the luteal phase was not followed either by changes in cycle length, endometrial morphology or hormone levels.

The results of a study conducted by Durand *et al* (2001) did not show significant alterations in serum hormone levels during the luteal phase when Levonelle-2 was administered the day after follicular rupture and similarly did not support any anti-implantation effect of the preparation. Marions *et al* (2002) found that the postovulatory treatment with two doses of 0.75 mg levonorgestrel, 12 hours apart, resulted in a cycle pattern, hormone levels and endometrial development similar to those of the untreated cycle.

Further it was well recognised that progesterone was necessary to maintain pregnancy and treatment of threatened miscarriage was with progesterone or progestogens. This again lent support to the premise that levonorgestrel would not act to disrupt an established pregnancy, but was conversely more likely to maintain it.

Finally, in the Judicial Review brought by The Society for the Protection of the Unborn Child (SPUC) against the Department of Health (where Schering Health Care was second defendant), The Honourable Mr Justice Munby found from the evidence provided at those proceedings and stated in his Judgment on 18 April 2002 that 'what is … clear ... is that

i. The morning after pill…cannot cause a fertilised egg which is implanted to de-implant –, that is, it cannot work after the process of implantation is complete.

ii. The morning after pill, if it is to be effective, has in any event to be taken at a time – not later than 72 hours after intercourse – when implantation will not have begun'.

Schering Health Care considered that the complainant's assertions concerning possible mechanisms of action of Levonelle had only the status of personal opinion and did not relate to either substantial scientific statements or matters of fact. As such, Schering Health Care did not regard them as substantive evidence on which any challenge to the SPC wording could be based.

PANEL RULING

The Panel noted that Schering Health Care had provided a leaflet 'A Health Professional's Guide to Emergency Hormonal Contraception' (ref L0311006) which had been prepared in November 2003 ie after the previous case, which involved *inter alia* a leaflet with the same title (ref LOH1032), had been considered. The leaflet referred to Levonelle-2 and was thus subject to the Code.

The Panel noted that Section 5.1 of the Levonelle-2 SPC stated that its precise mode of action was unknown. The SPC stated that at the recommended regimen it was thought to work mainly by preventing ovulation and fertilization if the intercourse had taken place in the preovulatory phase, when the likelihood of fertilization was the highest. It might also cause endometrial changes that discouraged implantation. It was not effective once the process of implantation had begun.

The Panel considered the additional data provided did not support a role for Levonelle-2 once implantation had occurred. The WHO Task Force on Postovulatory Methods of Fertility Regulation found that efficacy was significantly and inversely related to time since intercourse. Ho and Kwan found that pregnancy rates in patients who took the medicine within 24 hours were lower than those in patients who took it later. However, the study authors stated that probably because of the small patient numbers the difference was not statistically significant.

Croxatto *et al* reviewed research to understand how emergency contraception methods acted to prevent pregnancy. The authors stated that the fact than an entity or a process was altered by the treatment did not necessarily mean that it explained how pregnancy was prevented in real life situations. One of the complexities that researchers would have to deal with to find a thorough answer was that the mechanism might differ for the same emergency contraception treatment depending upon when it was given relative to the time of intercourse and time of ovulation. It was noted that there were few studies designed to look at the mechanism of action of levonorgestrel in emergency contraception and its exact mode of action was unknown. Various studies were discussed; Moggia *et al* (1974) proposed that the contraceptive effect was due to changes in the endometrium that prevented implantation. Similar comments were made in relation to Wang *et al* (1998) wherein in relation to the endometrium, preovulatory administration factors believed to be critical for implantation were changed in ways likely to alter endometrial receptivity. When appraising the possible modes of action Croxatto *et al* noted the inverse relationship between the intercourse-treatment interval and efficacy and stated that this lent support to a significant role of pre-fertilization mechanisms in its contraceptive effectiveness.

Durand *et al* assessed the mechanism of action of levonorgestrel stating that all emergency contraceptive medicines methods in use acted before implantation. The study did not support an anti-implantation contraceptive effect. Marions *et al* reported that their data suggested that the ovulation process was the main target for emergency contraception with levonorgestrel.

The Panel noted Schering Health Care's comments regarding the use of progesterone or progestogens for the treatment of threatened miscarriage. The Panel also noted, however, that the British National Formulary, September 2003, stated that there was no evidence of benefit and that progestogens were not recommended for such use.

The Panel noted the statement in the Levonelle-2 SPC that the precise mechanism of action was unknown. This was reflected in the additional data provided.

In relation to the leaflet, 'A Health Professional's Guide to Emergency Contraception', the claim 'It is not effective once the process of implantation has begun' appeared within a section entitled 'How does it work'. The claim was taken from the Levonelle-2 SPC. The preceding paragraph in the leaflet described in general terms the mechanism of action of emergency contraception stating that 'The precise mode of action is unknown, however emergency hormonal contraception is thought to work mainly by delaying or preventing ovulation and fertilization …. It may also cause endometrial changes that discourage implantation'. This was referenced to the Levonelle SPC.

The Panel noted the complainant's comments about the implantation process but considered that, given the statement in the SPC and the additional data provided, the statement in the leaflet was not unacceptable. No breaches of Clauses 7.2 and 7.4 were ruled.

APPEAL BY THE COMPLAINANT

The complainant stated that the claim 'Levonelle-2 is not effective once the process of implantation has begun' had only the status of personal opinion as it was only supported by indirect evidence. The complainant maintained that Schering Health Care should not use the claim unless it could provide conclusive direct evidence to confirm it.

The complainant noted the theory of how Levonelle-2 was thought to work and that the Honourable Mr Justice Munby stated in his judgement that Levonelle-2 had to be taken not later than 72 hours after intercourse when one would hope implantation would not have begun. In clinical practice however the process of implantation could very well have already begun at the time a patient requested Levonelle-2. The complainant noted, for example, that on numerous occasions even in his own clinical experience, women had requested the post coital pill within 72 hours of their latest intercourse, when however, more thorough questioning revealed that they had failed to mention that they had been having regular unprotected intercourse in the preceding days or weeks. Therefore if a doctor failed to take a thorough history before prescribing Levonelle-2, as might happen, or if the woman was not accurate in the timing she provided the doctor, there could be a blastocyst in the early stages of implantation at the same time as the blood and tissue levels of Levonelle-2 were rising to their peak.

The complainant stated that as the research submitted by Schering Health Care confirmed that Levonelle-2 caused adverse endometrial changes and even decidual necrosis had been reported (by the mechanism set out in his complaint) the process of implantation might be affected and cause a blastocyst which was in the early stages of implantation to 'de-implant'. Therefore, as Schering Health Care could not provide any direct evidence to prove otherwise the company should not make that claim.

The complainant highlighted two errors:

Firstly, if the quote provided was accurate the Honourable Mr Justice Munby had made a clear error in his judgement in that he talked about a 'fertilised egg' implanting: In fact the human being was a two hundred celled blastocyst by the time he or she implanted, whereas a fertilised egg was a human being at the single celled stage which was as yet incapable of implanting.

Secondly, applying the accepted definition of pregnancy; 'a woman having developing young in the womb', as soon as a woman had a fertilised egg inside her which began developing, she was pregnant. Therefore knowing that Levonelle-2 did not prevent an egg from being fertilised once released, Schering Health Care was technically incorrect to claim that Levonelle-2 'prevents pregnancy' as if it failed to prevent ovulation and the egg was fertilised, or it was given after ovulation had occurred and the egg was fertilised then it would not have prevented pregnancy at all as the woman would have a developing young human being inside her.

COMMENTS FROM SCHERING HEALTH CARE

Schering Health Care provided no further comments in response to the appeal.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant stated that, in view of the absence of direct, human, *in vivo*, research evidence provided by Schering Health Care, he was still unsure as to why the Panel had failed to rule against Schering Health Care regarding the statement in the SPC.

'It is not effective once the process of implantation has begun' (SPC, Health Professional's Guide to EC).

The complainant was puzzled as to why Schering Health Care had failed to provide him with a copy of the registration submission document specifically pertaining to the claims at issue.

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Schering Health Care's representatives stated at the appeal hearing that the company did not have access to the registration dossier; this was held by Gedeon Richter Ltd which held the licence.

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APPEAL BOARD RULING

The Appeal Board noted that in the Nygren and Johansson study (1975) certain synthetic gestagens had been given orally during 25 early, human pregnancies. The abstract stated that two women aborted after the treatment but judging from the hormonal levels these pregnancies were abnormal and would probably have aborted regardless of the treatment. The complainant pointed out that Nygren and Johansson reported that necrosis was found microscopically near chorionic invasive cells.

The Appeal Board noted that the mechanism of action of Levonelle was incompletely understood. Studies in

humans to obtain direct evidence on the process would not be ethical. Schering Health Care referred to the data showing the inverse relationship between efficacy and length of time from intercourse ie that pregnancy rates increased with time and submitted that this was a strong indication of the prefertilization mode of action and did not support the existence of the mechanism of any action after fertilization.

The Appeal Board noted that Section 5.1 of the Levonelle-2 SPC stated that its precise mode of action was unknown. The SPC stated that at the recommended regimen it was thought to work mainly by preventing ovulation and fertilization if the intercourse had taken place in the preovulatory phase, when the likelihood of fertilization was the highest. It might also cause endometrial changes that discouraged implantation. It was not effective once the process of implantation had begun.

The Appeal Board noted that the statement 'It is not effective once the process of implantation has begun' appeared within a section entitled 'How does it work' of the leaflet in question. The statement was taken from the Levonelle-2 SPC. The preceding paragraph in the leaflet described in general terms the mechanism of action of emergency contraception stating that 'The precise mode of action is unknown, however emergency hormonal contraception is thought to work mainly by delaying or preventing ovulation and fertilization …. It may also cause endometrial changes that discourage implantation'. This was referenced to the Levonelle SPC.

The Appeal Board considered that the context of the statement was an important factor. It was included in a detailed guide for health professionals and the relevant section gave full information consistent with the Levonelle-2 SPC about what was known about the mechanism of action.

On balance the Appeal Board considered that, given the SPC, the additional data provided and its context, the statement at issue was not unacceptable. No breaches of Clauses 7.2 and 7.4 were ruled. The appeal was unsuccessful.

Complaint received **27 February 2004**

Case completed **13 May 2004**

CASE AUTH/1561/3/04

GENERAL PRACTITIONER v WYETH

Promotion of Zoton FasTab

A general practitioner complained that Wyeth was repeatedly contacting many practices offering to change repeat prescriptions on the General Practice Administration System for Scotland (GPASS) for Zoton to Zoton FasTab (lansoprazole oro-dispersible tablets). The complainant alleged that the process involved company representatives changing the GPASS database in practices without the consent of patients. The complainant stated that the pretext for switching to Zoton FasTab was that it was 10% cheaper than Zoton and of equal efficacy and, therefore, was more cost effective. The complainant alleged that this was highly misleading as Zoton would come off patent this year and the tariff would fall, as generic alternatives became available. The complainant queried whether this was a marketing exercise designed to maintain profits and market share by Wyeth and alleged that Wyeth had breached the Code.

The Panel noted that the booklet provided to prescribers, entitled 'Lansoprazole prescribing. Formulary based implementation service pack', featured the Zoton FasTab product logo on the bottom right-hand corner of the front cover and included prescribing information. The booklet explained the service; the first stage required the practice to 'agree requirement for all patients currently on lansoprazole to be identified and where appropriate changed to lansoprazole oro-dispersible tablets'. The GP was required to sign a booking and consent form requesting a review by a GP Systems Specialist (GPSS). The signatory agreed that the Wyeth sponsored GPSS would require access to the computer; stated that the GPs were responsible for deciding whether access to the patients' electronic notes could be given for this purpose and referred to confidentiality. The GPSS would complete a formulary spreadsheet which the GP would then initial and sign to authorize a medication change. The GPSS implemented these recommendations, generated any prescriptions, patient letters and updates to patient notes.

The Panel considered that the service was part of the promotion of Zoton FasTab; it was not described as anything else in the material. The Panel noted Wyeth's submission that Zoton FasTab was 10% less expensive than Zoton capsules. Switching patients from Zoton capsules to Zoton FasTab was thus a less expensive way of prescribing Zoton. Companies could of course promote products on the basis of cost and it was not unreasonable to note savings that a practice might make by switching from one product to another. The difficulty was when the company paid directly or indirectly for those changes to be made because then the company's actions amounted to it paying to boost the prescription of a specific medicine. In the Panel's view it was immaterial that the two medicines at issue were marketed by the same company. The provision of the service by Wyeth would benefit a practice by saving it the expense of carrying out the switch itself. The arrangements amounted to a pecuniary advantage given as an inducement to prescribe Zoton FasTab. The Panel thus ruled a breach of the Code. High standards had not been maintained. A breach of the Code was ruled. The Panel noted that the representatives had offered the service but had not been involved in changing prescriptions as this had been carried out by a third party on behalf of Wyeth. The Panel thus ruled no breach of the Code. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved for particular censure.

A general practitioner complained about the promotion of Zoton FasTab (lansoprazole oro-dispersible tablets) by Wyeth Pharmaceuticals.

COMPLAINT

The complainant was concerned that Wyeth was repeatedly contacting many practices in his local area, and he assumed across the UK, offering to change repeat prescriptions on the General Practice Administration System for Scotland (GPASS) for Zoton to Zoton FasTab. This was a practice known as 'switching' and had been used by other companies in the past. The process involved company representatives changing the GPASS database in practices without the consent of patients. The pretext for switching to Zoton FasTab was that this was 10% cheaper than Zoton and of equal efficacy and, therefore, was more cost effective.

The complainant alleged that this was highly misleading. Zoton would come off patent this year and the tariff would fall, as generic alternatives became available. Within a year or so FasTab in fact would be relatively more expensive and the NHS would not benefit from the move to generic costings. The complainant queried whether this was a marketing exercise designed to maintain profits and market share by Wyeth and alleged that Wyeth had breached the Code and misled medical practices.

When writing to Wyeth the Authority asked it to respond in relation to Clauses 2, 9.1, 15.2 and 18.1 of the Code.

RESPONSE

Wyeth submitted that as the complainant made no specific allegations as such against the company and its activities, it was difficult for it to do more than provide the materials requested and state that it did not accept that it was in breach of the Code in relation to any aspect of its Formulary Based Implementation (FBI) Service that it appeared the complainant was concerned about.

The FBI Service was provided on request to those GPs who wished to implement computerised revisions to patient medication. In this case it was available to those who wished to take the benefit of cost savings available in relation to patients prescribed lansoprazole. It effected a dose for dose switch from Zoton capsules to Zoton FasTab; in clinical terms the two formulations were bioequivalent and, in addition to being 10% cheaper, Zoton FasTab offered additional

convenience to patients as it could be taken with or without water (unlike Zoton capsules). The service was provided to the GP practice not by Wyeth representatives but by appropriately qualified specialist IT contractors (known as GP System Specialists, GPSS) engaged by Wyeth through a third party. Wyeth provided the GP material for this service together with pages from its sales representatives' briefing and training document, the Action Plan, as this further described the service and its implementation.

With regard to the allegation that it was repeatedly contacting practices offering to change repeat prescription on GPASS for Zoton to Zoton FasTab, Wyeth stated that it was making the FBI Service available as described above. Wyeth denied that it was making repeat calls such that it would be in breach of the requirements of the Code.

In response to the allegation that Wyeth representatives were changing GPASS databases without the consent of patients, Wyeth noted that none of its sales representatives were involved in implementing the FBI Service. Wyeth had involvement in the FBI Service only through the GPSS making database changes in response to requests to do so from the GPs concerned. Patient consent was the responsibility of the instructing GPs, not Wyeth. However, Wyeth facilitated GP communication with patients by proposing suggested text for such letters.

Wyeth denied that it was using a misleading pretext for its switch programme. Zoton FasTab was 10% cheaper than Zoton capsules and Wyeth's service enabled the requesting GP to benefit quickly from the cost savings available. It was not the case that Zoton would come off patent this year.

Wyeth did not accept that it was in breach of any of the requirements of the Code in relation to the FBI Service.

PANEL RULING

The Panel noted that the booklet provided to prescribers, entitled 'Lansoprazole prescribing. Formulary based implementation service pack', (ref ZZ0T3413) featured the Zoton FasTab product logo on the bottom right-hand corner of the front cover and prescribing information on the outside back cover.

The booklet explained what the service entailed; the first stage required the practice to 'agree requirement for all patients currently on lansoprazole to be identified and where appropriate changed to lansoprazole oro-dispersible tablets'. The GP was required to sign a booking and consent form requesting a review by a GPSS. The representatives' briefing document explained that all partners were required to sign the consent form unless the practice had a designated partner authorized to make formulary decisions on behalf of the whole practice. The signatory agreed that the Wyeth sponsored GPSS would require access to the computer; stated that the GPs were responsible for deciding whether access to the patients' electronic notes could be given for this purpose and referred to confidentiality. The GPSS would complete a formulary spreadsheet which the GP would then initial and sign to authorize a medication change. The GPSS implemented these recommendations, generated any prescriptions, patient letters and updates to patient notes.

The Panel noted Wyeth's submission that Zoton FasTab was 10% cheaper than Zoton capsules and that Zoton did not come off patent this year. The Panel did not have before it any of the promotional material or representatives' briefing material in relation to the comparative cost of Zoton capsules and Zoton FasTab.

The Panel considered that the service was part of the promotion of Zoton FasTab; it was not described as anything else in the material. The service could thus not benefit from the supplementary information to Clause 18.1 regarding the provision of medical and educational goods and services. The Panel noted Wyeth's submission that Zoton FasTab was 10% less expensive than Zoton capsules. Switching patients from Zoton capsules to Zoton FasTab was thus a less expensive way of prescribing Zoton. Companies could of course promote products on the basis of cost and it was not unreasonable to note savings that a practice might make by switching from one product to another. The difficulty was when the company paid directly or indirectly for those changes to be made because then the company's actions amounted to it paying to boost the prescription of a specific medicine. In this regard the Panel noted that the switch programme at issue involved two products marketed by the same company; prescriptions for Zoton FasTab were not being generated at the expense of another company's product. Nonetheless, Clause 18.1 of the Code stated that 'No gift, benefit in kind or pecuniary advantage shall be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend or buy **any** medicine, subject to the provisions of Clause 18.2'. Thus in the Panel's view it was immaterial that the two medicines at issue were marketed by the same company. The provision of the FBI Service by Wyeth would benefit a practice by saving it the expense of carrying out the switch itself. The arrangements amounted to a pecuniary advantage given as an inducement to prescribe Zoton FasTab. The Panel thus ruled a breach of Clause 18.1 of the Code. High standards had not been maintained. A breach of Clause 9.1 was ruled. The Panel noted that the representatives had offered the service but had not been involved in changing prescriptions as this had been carried out by a third party on behalf of Wyeth. The Panel thus ruled no breach of Clause 15.2. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code which was reserved for particular censure

Complaint received **11 March 2004**

Case completed **7 June 2004**

PRIMARY CARE TRUST CHIEF PHARMACIST v TRINITY

Conduct of representatives

The chief pharmacist at a primary care trust (PCT) complained about the conduct of representatives from Trinity. About ten months ago three of the surgeries in the PCT informed the complainant that the local Trinity representative had contacted them and informed them that she was working on behalf of the complainant and offered to change some of the medicines in the surgeries to Trinity's products. In one surgery she actually had implemented some changes. The complainant informed the surgeries that the representative was not working on her behalf.

The complainant expressed her concerns to the representative and told her that she was making changes in the surgeries by false pretences. The representative subsequently visited the complainant accompanied by one of her managers. They reassured her that the surgeries in question had misunderstood them, apologized and promised that it would never happen again. Unfortunately their actions were repeated last month and the complainant was informed by the surgeries that Trinity's new representative had approached them and once again pretended that she was acting on the complainant's behalf.

The complainant was exceptionally unhappy with this given that this was the second time that Trinity had done this in less than a year. The complainant strongly believed that this type of behaviour must stop otherwise the working relationship with primary care organisations and pharmaceutical companies would suffer badly.

The complainant did not believe it was the representative's fault, but that it was the managers who pressurised the representative to unethical behaviour. The reason for this was that when she asked the previous representative to stop acting unprofessionally ten months ago, her manager saw the complainant and they said they would make sure it did not happen again and the new representative had done it again.

The complainant stated that it was happening all over the country; one PCT had informed her that it was happening in its area but it did not have solid evidence. Another said that it had reported Trinity to the Authority two years ago. The complainant had the names of other PCTs which had had bad experiences with Trinity.

The complainant wrote further and stated that she had attended a hospital's drug and therapeutic committee and was informed by its pharmacist that Trinity had contacted it and reassured it that Trinity's isosorbide-monitrate was the medicine of choice in primary care in the county and offered to give them a good deal if they got their stock from Trinity. This information was incorrect and Trinity's medicine was not on the local formulary.

The Panel noted that the parties' accounts of what took place differed and that it was difficult in such cases to know exactly what had transpired. A judgement had to be made on the evidence which was available, bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint.

It appeared from the papers provided that the complainant had had a close working relationship with one of the representatives from Trinity in relation to arrangements for audits taking place within the PCT; at one point the complainant had contacted a doctor, who had previously not granted one of the representatives an interview, to ask him to see the representative. The complainant had also provided one of the representatives with a reference describing her as 'a great asset to me'. At times the emails between the two parties referred to personal matters. The complainant had invoiced Trinity on 9 July 2003 for £105 for 'sponsorship monies towards administrative cost to do calcium and vitamin D audit'. An email from a representative to the complainant dated 28 September 2002 referred to dropping 'a cheque in'. In the Panel's view some people might have got the impression that the complainant and the representatives from Trinity were cooperating as a team.

The Panel considered that it was impossible to know where the truth lay. The complainant had alleged that the representatives were telling surgeries that they were working on behalf of the PCT. Correspondence produced by Trinity indicated that customers were clear that the representatives were from the company. Given the parties' differing accounts the Panel was not in a position to determine what had happened. The Panel therefore ruled no breach of the Code.

The chief pharmacist at a primary care trust (PCT) complained about the conduct of representatives from Trinity Pharmaceuticals Ltd.

COMPLAINT

The complainant strongly believed in working in partnership with the pharmaceutical industry; she viewed it as an important stakeholder in the NHS. She had always treated the NHS liaison managers from the companies with respect and worked with them in partnership. However she had recently had a very unpleasant experience with Trinity.

About ten months ago three of the surgeries in the complainant's PCT informed her that the local Trinity representative had contacted them and informed them that she was working on behalf of the complainant and offered to change some of the medicines in the surgeries to Trinity's products. In one surgery she actually had implemented some changes. The complainant informed the surgeries that the representative was not working on her behalf.

The complainant expressed her concerns to the representative and told her that she was making changes in the surgeries by false pretences. The representative subsequently visited the complainant accompanied by one of her managers. They reassured

her that the surgeries in question had misunderstood them. They apologized and promised that it would never happen again. The complainant accepted their apologies. Unfortunately their actions were repeated last month, and the complainant was informed by the surgeries that Trinity's new representative had approached them and once again pretended that she was acting on the complainant's behalf.

The complainant was exceptionally unhappy with this given that this was the second time that Trinity had done this in less than a year. She had contacted other PCTs and was horrified to find out that her PCT had not been the only victim of Trinity; the complainant knew of four more PCTs that had the same experience with Trinity.

The complainant stated that she had cancelled her appointment with the Trinity representative and asked her not to contact her. However several messages had been left on her answer phone.

The complainant strongly believed that this type of behaviour must stop as otherwise the working relationship with primary care organisations and pharmaceutical companies would suffer badly. After these incidents she felt very uncomfortable to work with the pharmaceutical companies, which was a shame as she used to have trust and respect for the industry people she had worked with.

In response to a request for further information, the complainant stated that although she had asked Trinity not to contact her until this matter was sorted, she had received lots of messages from the company.

The complainant had also asked Trinity not to contact the surgeries in the PCT until this matter was resolved, however it had contacted the GPs and tried to put pressure on them so that they could influence the complainant and stop her from complaining. The GPs were not happy to be put under pressure and they told the complainant what Trinity was doing.

Trinity had emailed one GP in her PCT to ask for the PCT formulary. The complainant explained that this formulary was internal and owned by the PCT, in particular the complainant said that the GP would need her permission to pass it on.

The complainant named the surgeries which had been unhappy with Trinity's action ten months ago and also named the representative from that time. The name of the current representative was also given.

The complainant stated that she did not believe it was the representative's fault, but that it was the managers who pressurised the representative to unethical behaviour. The reason for this was that when she asked the previous representative to stop acting unprofessionally ten months ago, her manager saw the complainant and they said they would make sure it did not happen again and the new representative had done it again.

The complainant stated that it was happening all over the country; one PCT had informed her that it was happening in its area but it did not have solid evidence against the company. Another said that it had reported Trinity to the Authority two years ago. The complainant had the names of other PCTs which had had bad experiences with Trinity, however she was waiting for their permission to pass their names to the Authority.

The complainant wrote with further information and stated that she had attended a hospital drug and therapeutic committee and was informed by its pharmacist that Trinity had contacted it and reassured it that Trinity's isosorbide-monitrate was the medicine of choice in primary care in the county and offered to give them a good deal if they got their stock from Trinity. This information was incorrect and Trinity's medicine was not on the local formulary.

When writing to advise Trinity of the complaint the Authority asked that when considering events which occurred after 1 July 2003 it respond in relation to the requirements of Clauses 2, 9.1 and 15.2 of the 2003 edition of the Code. It was noted that although the events of ten months ago would fall under the requirements of the 2001 edition of the Code the same clauses of that Code would apply; the part of Clause 9.1 which was relevant was that pertaining to high standards.

RESPONSE

Trinity explained that on 17 November 2003, two of its representatives met, by appointment, with the complainant. The outcome of the discussion was that both Adcal D3 (Strakan's calcium and vitamin D3 supplement) and Calfovit D3 would be added to the PCT incentive by the complainant until March 2004 and would remain on the PCT formulary after that date. The complainant stated that she was happy for Trinity to actively promote Calfovit D3 in her local area but suggested that the representative wait until after Christmas so patients didn't get sick on turkey and blame it on their medicine.

In January 2004 the current representative actively promoted Calfovit D3 as agreed. On 27 January she had an appointment with the practice manager at a surgery. The practice manager said that the surgery did not like industry audits but Trinity had conducted such an audit 8 years previously and the outcome had been positive, so a respiratory and calcium supplement audit was booked for 12 February at the practice manager's request. The representative and the regional business manager carried out the respiratory and calcium supplement audit on 12 February.

The practice manager requested a cost savings analysis as well and a date was booked for feedback. The practice manager was impressed with the cost savings analysis and agreed to talk to the practice partners about savings. She suggested the representative call the branch surgery to arrange to see the lead GP to pursue this. On 24 February the representative telephoned the practice manager for feedback from the practice meeting at which the cost savings analysis was to have been discussed. The practice manager stated that the meeting agenda was too busy to give the report adequate consideration, but again emphasised the need for the representative to see the branch surgery lead GP.

On 3 March the representative saw the lead GP who said that she would like to put the 35 patients

currently taking ergocalciferol identified during the calcium supplement audit on to Calfovit D3, but as Calfovit D3 was not on the PCT formulary, she could not. The representative informed her that both Adcal D3 and Calfovit D3 were on the PCT formulary as alternatives. The representative further told her that she had seen the complainant in November and that the complainant knew she was working in the area after Christmas (as agreed at the meeting of 17 November). The representative advised her that both treatments were in the PCT incentive (as she was informed by the complainant at their meeting on 17 November) and that she had a further appointment with the complainant on 16 March to discuss future plans. The lead GP told the representative that she had not previously heard of Calfovit D3 but liked the idea of a drink and as both Calfovit D3 and Adcal D3 were in the PCT incentive, she wanted those patients currently taking ergocalciferol changed to Calfovit D3. She also agreed to change 29 patients identified in the asthma audit to Pulvinal.

Also on 3 March the representative called the practice manager to inform her of the lead GP's request and book a date for the Trinity switch coordinator to attend the surgery and effect the requested changes. The representative told the practice manager that once she had the patient letters written and signed she would go to the surgery to show her. The following day the practice manager telephoned the representative. Apparently the complainant had seen the lead GP and advised her not to make the changes as agreed as she would be making further changes directed from the PCT. The GP had asked the practice manager to call the representative as soon as possible so that she did not prepare any work unnecessarily.

On 5 March the representative received the following email from the complainant:

> 'I am very unhappy about the recent situation that your company has told the surgeries that you are acting on my behalf and trying to change the patients over to your product. I had this problem before when [the previous representative] was working in this area. Under no circumstances you have any blessing from me to go to the surgeries and changing the patients over as the matter of fact, I do not want you in the [named] PCTs surgeries at all.
>
> I would like to cancel my appointment with you as I told [the previous representative's] manager last year that I do not like people to do anything on my behalf, I am seeking advice on how to go forward and act to stop your company repeatingly misleading my GPs.
>
> I may even take all your products off our formulary as your action is very unethical.'

The representative immediately called the complainant and left two voice mails explaining what had happened with the lead GP and the branch surgery. The representative requested to keep the appointment on 16 March and asked that the complainant return the call. On 8 March the representative rang the complainant leaving a voice mail, repeating the situation and again asking her to return her call.

The representative subsequently attended an appointment with a GP where she was shown an email from the PCT prescribing lead which stated that the PCT was not working with Trinity and if anyone was approached by Trinity and asked to change medications on behalf of the PCT then they should report this to the prescribing lead. (The email implied that Trinity had been doing this.)

On 10 March the representative telephoned the complainant and someone else answered the telephone and agreed to give a message to the complainant.

The representative called the prescribing lead and told him that she had seen his email and explained the facts as they occurred. She told him that she had never said or implied that she worked for anyone other than Trinity. The prescribing lead said this was not the information he had been given and stated, 'his email hadn't helped'. He apologized for not having the time to investigate this before he sent the email. He told the representative that he was satisfied with what she had told him and that his email had asked for 'evidence' which he had not, and did not expect to receive from anyone in the PCT. The representative told him that the complainant had said she would consider taking the Trinity products off the formulary to which he replied that whilst there would be a 'revamp' in the asthma prescribing, he had no intention of removing Calfovit D3 as he liked it. If the product were removed, he would wish to know why. He told the representative that he did not have a problem with her or Trinity and that he would work with the company if and when something suitable arose.

The representative telephoned the practice manager who said she was never in any doubt about who the representative worked for. She knew she was not from the PCT or doing work on its behalf. The practice manager told the representative there was no bad feeling whatsoever with her or Trinity and she had never thought ill of the company anyway.

On 11 March the previous representative telephoned the complainant, who said that this was the second time Trinity had done this, but failed to mention that on the previous occasion she had apologized. The complainant said she could not be seen associating with Trinity as she had her reputation to consider so she would not keep the appointment on 16 March. The situation was explained to the prescribing lead and he was asked to retract the email sent to the PCT – he said it would be a PCT members' decision once they were sure that no evidence was found. This would be recorded in the minutes and sent to the 'Professional Executive Committee'. He admitted that they would look stupid if there was not any evidence.

The prescribing lead said he did not want to get 'embroiled in politics' but would talk to the complainant at their meeting on Monday. He said that Trinity had worked with the complainant before when surgeries, such as his own, asked for audits and changes to be carried out.

Trinity stated that the actions ten months ago followed similar contact between the previous representative and the complainant. The complainant had directed the representative to conduct audits in

the surgeries to include modified release (MR) diclofenac (the complainant wanted to identify areas she could make savings such as moving patients from MR diclofenac to non-MR three times a day), since these were her most overspent surgeries. The complainant then requested the representative supply her with copies of the subsequent audit results.

No action was taken as a result of the complainant's original complaint, since she addressed this to the representative, who subsequently attended a meeting with her and her manager on which occasion the complainant apologised for sending the original note, but explained she had been accused of being too close to Trinity by some GPs. As such, Trinity was unaware she had an issue with the company; its activities or its representatives.

In respect of the complainant's accusation regarding a hospital, Trinity provided a copy of correspondence following a meeting on 12 August at which the current and previous representatives explained that Monomax XL tablets were on the formulary in the PCT and that Monomax XL was a less expensive option than the currently prescribed isosorbide mononitrate preparation. Subsequent contact in the hospital was with the drug information pharmacist, who requested a draft contract for the supply of Monomax XL.

Trinity did not consider that any aspect of its representatives' activities on either occasion constituted a breach of Clauses 2, 9.1 or 15.2. The company was at a complete loss to understand the complainant's allegations, and could only conclude from interviewing the representatives involved, and reviewing the correspondence between the parties, that the representative had fallen foul of the complainant because she declined her invitation to sponsor a meeting.

FURTHER COMMENTS FROM THE COMPLAINANT

In response to a request for further information the complainant stated that she agreed with Trinity's account of the meeting of 17 November as far as its product was in the formulary and Trinity could discuss it with GPs as other companies would do. However the complainant emphasized that what had happened before should not be repeated and the representatives agreed.

With regard to January 2004 when Trinity stated that the representative was actively promoting Calfovit in the area as agreed, the complainant stated that it was never agreed that the representative should tell surgeries that she was working on behalf of the complainant. The complainant had agreed that Trinity like other companies could work with surgeries and it would be the surgeries that would decide if they were going to use Trinity's products.

The complainant could not comment on other meetings as she was not present. However on 3 March the lead GP contacted the complainant to ask if she had instructed Trinity to work on her behalf. The complainant told her that under no circumstances had she done so. The GP told the complainant that that was what Trinity's representatives had told her surgery. The complainant immediately reported this to the Medicines Management and Prescribing Group via email.

The complainant stated that she was happy with her email of 5 March to the current representative. On 8 March the current representative rang the complainant three times on her work and her mobile number. Then the previous representative called her on her mobile telling her that the current representative was very sorry and that the complainant should talk to her as she was very unhappy. The complainant told her that she would not be returning any call from Trinity until she had decided what action she should take regarding the recent problem. The complainant asked her to tell the current representative not to call. The following day the complainant had two further voice messages from the current representative and a message to call her urgently which she did not. Then the previous representative got an advisor from another PCT calling and trying to put pressure on the complainant.

The complainant stated that the lead GP had contacted her sometime in early March to tell her that the current representative and her manager were trying to change her mind and were asking her to contact the complainant to state that she was happy with Trinity and she had never had any problem with them. However the GP told the complainant that she had told Trinity that she would have to tell the truth.

The complainant could not comment on Trinity's conversation with the prescribing lead. He emailed the complainant on 10 March and told her that 'someone sent my email regarding Trinity, that I sent to all the Drs, to Trinity…'. He was extremely annoyed about this and told the complainant that he was being pressurized by Trinity to stop the email.

The email from the prescribing lead asked for copies of any correspondence from Trinity which suggested that it was switching patients on behalf of the PCT. The email further stated that the PCT was not currently working with Trinity.

An email from the complainant to him stated that in the last two years that she had been in the PCT, she had never endorsed Trinity working in the surgeries; she had sent an email out to all the GPs informing them that Trinity did not work on behalf of the PCT.

The complainant noted that she did not ask the previous representative to do any audit for her. The representative had told the complainant that she was working with surgeries and helping to change some modified release product. The complainant asked her not to change anyone on diclofenac MR (which she did in a surgery and caused the first complaint, as she told the surgery that she was acting on the complainant's behalf) as she was doing an audit to move the patients to standard release. The complainant even showed the representative the minutes of the prescribing group which stated that the complainant strongly recommended against changing patients on diclofenac MR to Trinity's products until she had finished the NSAID audit.

The complainant stated that the previous representative had said that she would like to work

with the PCT as well as the surgeries and she would forward any information that she might think would be useful to the complainant. The complainant thanked her but noted that she had never asked her to provide her with any information on her audits. The previous representative also discussed Trinity's asthma product and the complainant told her that she had issues over the inhaler as she considered that it might be difficult to use. However the complainant would be happy if the GPs and nurses were happy with it. The complainant suggested that she should see a particular GP as he was an expert in asthma but was told by her that he had not given her an appointment. The complainant emailed him to ask him to see the previous representative.

The complainant stated that the only reason she did not report Trinity before was that the previous representative and her manager apologised to her and told her that it would not happen again. The complainant had never apologised to anybody from Trinity. The manager was aware of the complainant's concerns and he promised that it would not happen again. The previous representative tried very hard to become a friend and gave the complainant an invitation to her wedding which the complainant declined.

The complainant noted that she had been told that the only reason consultants wanted the Trinity product was because Trinity told them that it was in the PCT formulary.

The complainant noted that she had asked the current representative for sponsorship and provided a copy of the response, noting that she had not exactly declined the request.

The complainant noted that she had written a letter of recommendation for the previous representative. As she was unwell, the letter was based on the fact that at that time she was working ethically. The complainant had also given the representative the name of some of the surgeries which she thought would look at the inhaler and give their verdict to her.

In summary, the complainant stated that she had never asked the previous representative to act on her behalf and do any audit; she had not worked with her any differently than with any other company. The complainant had told her over and over that she should not be telling GPs that she was acting on her behalf. Under no circumstances would anybody have seen the complainant's relationship with her as friendship as she worked with industry closely and treated all of them with respect.

The complainant stated that she was very unhappy that Trinity had suggested that she would get mad because the company did not sponsor a meeting. The complainant noted that she was a professional and took these kind of comments very seriously and considered them slanderous.

The complainant still felt very strongly about Trinity's behaviour and even more strongly now as it was trying to cover its unethical acts. The complainant stated that as an industry friendly advisor she might have to review her working relationship with industry.

The complainant provided copies of emails from doctors stating that Trinity was claiming to be working on behalf of the PCT and also from other pharmaceutical advisors stating that Trinity had done the same thing in their PCTs.

In a further letter to the Authority the complainant emphasized that she had never worked with anybody from Trinity as a team, however she did work with industry and due to her nature she was friendly and nice to people from industry. Her understanding of the previous representative's audits had been that the surgeries were happy about them and she was just informing of the outcomes. The complainant had never stopped the surgeries working with industry as long as it was transparent and the surgeries knew that they were the ones agreeing to the work. However Trinity had been misinforming the practices. The complainant produced a copy of an email sent to the previous representative on 28 May. The email expressed the complainant's concern about the way Trinity had approached surgeries and stated that the company was working on behalf of the complainant. The email stated that the representative had been asked specifically not to change any patient on diclofenac MR. The email ended with the statement 'your approach is damaging to PCT and Pharmaceutical Industry relationship'. The complainant noted that this strongly worded email was sent to the previous representative before she knew the current one so how could she be angry with the current representative even before she met her? The complainant questioned why Trinity had not provided the Authority with a copy of the email. The complainant alleged that the company was trying to discredit her.

The complainant noted that on several occasions the previous representative had offered to buy her office a colour printer and facsimile machines or lunch; all offers were refused.

The complainant also noted that both representatives had stated that there was no need to declare Trinity's sponsorship on documents which they had offered to get printed for a local meeting.

The complainant noted that she had supported the previous representative when she had been unwell and had family difficulties but put this down to her warm personality. The complainant stated that she was a friendly person and was always invited to attend the ABPI dinners and people's personal parties but that she was a professional and acted ethically.

PANEL RULING

The Panel noted that the parties' accounts of what took place differed and that it was difficult in such cases to know exactly what had transpired. A judgement had to be made on the evidence which was available, bearing in mind that extreme dissatisfaction was usually necessary on the part of an individual before he or she was moved to actually submit a complaint.

It appeared from the papers provided that the complainant had had a close working relationship with one of the representatives from Trinity in relation

to arrangements for audits taking place within the PCT; at one point the complainant had contacted a doctor, who had previously not granted one of the representatives an interview, to ask him to see the representative. The complainant had also provided one of the representatives with a reference describing her as 'a great asset to me'. At times the emails between the two parties referred to personal matters. The complainant had invoiced Trinity on 9 July 2003 for £105 for 'sponsorship monies towards administrative cost to do calcium and vitamin D audit'. An email from the previous representative to the complainant dated 28 September 2002 referred to dropping 'a cheque in'. In the Panel's view some people might have got the impression that the complainant and the representatives from Trinity were cooperating as a team.

The Panel considered that it was impossible to know where the truth lay. The complainant had alleged that the representatives were telling surgeries that they were working on behalf of the PCT. Correspondence produced by Trinity indicated that customers were clear that the representatives were from the company. Given the parties' differing accounts the Panel was not in a position to determine what had happened. With regard to the events of ten months' ago, the Panel therefore ruled no breach of Clauses 2, 9.1 and 15.2 of the 2001 edition of the Code. With regard to the more recent events the Panel ruled no breach of Clauses 2, 9.1 and 15.2 of the 2003 edition of the Code.

Complaint received **16 March 2004**

Case completed **7 June 2004**

CASE AUTH/1563/3/04

GLAXOSMITHKLINE CONSUMER HEALTHCARE v PFIZER CONSUMER HEALTHCARE

Promotion of Nicorette

GlaxoSmithKline Consumer Healthcare complained about the promotion of Nicorette Patches by Pfizer Consumer Healthcare. The items at issue were an advertisement and a leavepiece. Nicorette Patches released nicotine over 16 hours. GlaxoSmithKline Consumer Healthcare marketed NiQuitin CQ Patches which delivered nicotine over 24 hours.

GlaxoSmithKline Consumer Healthcare stated that the headline 'Your patients don't smoke while they sleep, so why treat them as if they do?', which set the tone for the advertisement, was a valid question, but as Pfizer Consumer Healthcare made no effort to answer it the reader was left with the impression that there was no reason to give overnight nicotine. This was not a balanced, fair or objective evaluation of the evidence.

The Panel noted that Nicorette Patches were to be applied on waking (usually in the morning) and removed 16 hours later (usually at bedtime). NiQuitin Patches, however, were to be applied once a day, at the same time each day and worn continuously for 24 hours. The NiQuitin CQ Patch summary of product characteristics (SPC) stated that the patches could be removed before going to bed if desired but use for 24 hours was recommended to optimise the effect against morning cravings.

The Panel considered that the headline 'Your patients don't smoke while they sleep, so why treat them as if they do?' drew attention to the use of 16 hour as opposed to 24 hour patches. The advertisement was designed to promote Nicorette Patches and in doing so referred to one of the differences between Nicorette Patches and NiQuitin CQ Patches. The Panel did not consider that not answering the rhetorical question meant that the headline was either unbalanced or misleading as alleged. No breach of the Code was ruled.

GlaxoSmithKline noted that the claim 'Which helps your patients avoid the nocturnal nicotine dosing commonly associated with unnecessary sleep disturbance' appeared in the main body of the text and was immediately preceded by 'Nicorette 16 hour Patch is uniquely designed to deliver a full dose of nicotine only during normal waking hours'. The claim was asterisked to a footnote which read 'Nicorette 16 hour Patch is the only one not shown to cause sleep disturbance over and above placebo levels'.

GlaxoSmithKline Consumer Healthcare noted that sleep disturbance claims had been the subject of previous rulings and cited Case AUTH/1329/6/02 where a breach was ruled and Case AUTH/1380/10/02 where no breach was ruled.

GlaxoSmithKline Consumer Healthcare alleged that the claim 'Which helps your patients avoid the nocturnal nicotine dosing commonly associated with unnecessary sleep disturbance' gave an unbalanced view of sleep disturbance during smoking cessation. The visual was of a woman sleeping peacefully, inviting the reader to assume a good night's sleep on Nicorette patch. The advertisement did not make it sufficiently clear that sleep disturbance commonly occurred when quitting smoking, as it was one of the recognised symptoms of nicotine withdrawal, and that Nicorette 16 hour patch did not enable patients to avoid this sleep disturbance caused by nicotine withdrawal. Neither did it mention any of the studies showing an improvement or no change in sleep disturbance during smoking cessation when overnight nicotine was administered. In focussing solely on sleep disturbance, this campaign gave an

unbalanced view of nicotine patches, raising undue concern about 24 hour patch safety.

The Panel noted that smokers who stopped smoking were likely to experience sleep disturbance due to withdrawal from nicotine. Studies had shown no change to such sleep disturbance with Nicorette Patches; the claim in question was asterisked to a footnote which stated 'Nicorette 16 hour Patch is the only one not shown to cause sleep disturbance over and above placebo levels'. Sleep disturbance was not listed in the Nicorette Patch SPC as an undesirable effect of therapy. Conversely the Panel noted GlaxoSmithKline Consumer Healthcare's submission that sleep disturbance could occur in those using 24 hour patch therapy. Insomnia and abnormal dreams were listed in the NiQuitin Patch SPC as possible side effects of therapy, both of which occurred more frequently than with placebo. The SPC stated that NiQuitin patches could be removed before going to bed if required. The Panel considered that there were clear differences between Nicorette Patches and NiQuitin Patches in terms of their propensity to add to the sleep disturbance which occurred as a consequence of nicotine withdrawal. The Panel did not consider that focussing on sleep disturbance gave an unbalanced view of nicotine patches or raised undue concern about the safety of 24 hour patches as alleged. No breaches of the Code were ruled.

The Panel noted Pfizer Consumer Healthcare's submission that in the claim '[Nicorette] helps your patients avoid the nocturnal nicotine dosing commonly associated with unnecessary sleep disturbance' the word 'unnecessary' was included to distinguish between the sleep disturbance which was part and parcel of quitting and the additional disruption to sleep caused by nocturnal nicotine dosing. The Panel, however, did not consider that the claim adequately distinguished between the two types of sleep disturbance and considered that some readers would be left with the impression that those taking Nicorette would not have a disturbed night's sleep which was not necessarily so as they would continue to experience the sleep disruption caused by nicotine withdrawal. The footnote 'Nicorette 16 hour Patch is the only one not shown to cause sleep disturbance over and above placebo levels' did not negate the impression given. The expectation of a good night's sleep on Nicorette was strengthened by the visual of a woman sleeping peacefully in bed. On balance the Panel considered that the claim was misleading. A breach of the Code was ruled.

GlaxoSmithKline Consumer Healthcare alleged that the claim '… Nicorette 16 hour Patch also provides maximum craving control when patients are at their most vulnerable' was misleading because it could be interpreted in a number of ways. Firstly, Nicorette 16 hour patch did not provide 'maximum craving control'. Maximum craving control could easily be achieved by having a cigarette and completely relieving the craving. Pfizer Consumer Healthcare defined 'maximum' in terms of 'The time or period during which the highest point or degree is attained', rather than the amount of craving relief obtained. No data had been provided showing the level of craving control achieved throughout the day at various points to substantiate the claim. The second aspect was 'when patients are at their most vulnerable'. Most vulnerable to what? Cravings? Relapse? The two were not interchangeable and smokers did not necessarily relapse at a time when cravings were at their peak. Pfizer Consumer Healthcare appeared to be confusing cravings with relapse. Many patients were most vulnerable to cravings first thing in the morning when the Nicorette patch left a gap in protection. As morning craving was a predictor of relapse, even afternoon relapse, part of the solution might lie in the treatment of morning craving (Shiffman *et al* 1997). GlaxoSmithKline Consumer Healthcare agreed that patients might well be more vulnerable to relapse in the afternoon or evening, as there was more opportunity for lapsing, with exposure to others smoking, alcohol, and release from smoking restricted environments. However, Pfizer Consumer Healthcare had not provided data that Nicorette prevented relapse in the afternoon relative to placebo.

The Panel considered that it was not clear whether the claim '… Nicorette 16 hour Patch also provides maximum craving control when patients are at their most vulnerable' meant that Nicorette patches controlled cravings when they were at their worst ie in the morning, or controlled them when smokers were most vulnerable to relapsing ie afternoon/evening. Pfizer Consumer Healthcare had submitted that it was the latter. The Panel considered that the claim was ambiguous and misleading as alleged. A breach of the Code was ruled.

The leavepiece was entitled 'Nicorette Patch – specially designed for waking hours only' and featured two bar charts, one depicting incidence of sleep disturbance for Nicorette from two studies, Tønnesen *et al* (1999) and Sachs *et al* (1993), and the other depicting the incidence of sleep disturbance with a 24 hour patch ie NiQuitin, from two studies, ICRF General Practice Research Group and Richmond *et al* (1994). Sleep disturbance with Nicorette was shown to be similar to that of placebo ($p=ns$) at 5.4% in one study and 3.5% in the other. The incidence of sleep disturbance for the 24 hour patch was statistically significantly greater than placebo with 20.4% ($p<0.0001$) in one study and 26% ($p<0.03$) in the other.

GlaxoSmithKline Consumer Healthcare submitted that using the risk of sleep disturbance as the main promotional platform gave unwarranted clinical significance to this side effect. Most patients using a 24 hour patch would not suffer sleep disturbance. As discussed above even if they did it was very unlikely to warrant a change of therapy or discontinuation as the vast majority of sufferers reported their sleep disturbance as mild or moderate. Further, for a proportion of patients, sleep disturbance would be alleviated by using nicotine overnight.

GlaxoSmithKline Consumer Healthcare stated that the use of two bar charts side by side invited comparison when none could be made due to differences in the study conditions and data collection. The footnote 'Cochrane review meta-

analysis – a comprehensive overview, representative of the body of evidence for NRT use' under the bar charts was misleading. Reference to the Cochrane collaboration lent undue weight and credence; the reader would be falsely reassured that the Cochrane Collaboration supported this interpretation, when in fact Cochrane specifically indicated that it was inappropriate to compare the incidence of side effects due to inter-study variation.

The data quoted for Tønnesen *et al* were incorrect; n=3575 included patients from all 5 arms in the study, three of which were not consistent with the licensed particulars of Nicorette patch. Although 'insomnia' was quoted in the paper as 5.9% v 5.4%, the bar chart axis and remainder of the promotional piece referred to 'sleep disturbance'. In this study, nightmares were reported in 7% (15mg) v 6% for placebo, and vivid dreams were 18% v 15%. Both of these conditions were examples of sleep disturbance. The incorrect reference to 'sleep disturbance' provided a falsely low figure which was misleading.

The Panel noted that data from Tønnesen *et al*, which was included in the bar chart depicting sleep disturbance with Nicorette, appeared to relate to the whole study population ie n=3,575. The bar chart showed the figures of 5.4% and 5.9% for Nicorette and placebo respectively and so in that regard the data did not relate to the whole study population but only to those using either 15mg patches or placebo (n=2,145). It was thus inaccurate and misleading to label the chart n=3,575. The Panel ruled a breach of the Code.

The Panel considered that the presentation of the two bar charts invited comparison of the results contained therein. The data shown for the Nicorette 16 hour patch accorded with the balance of the evidence in so much as there was no significant difference between active and placebo with regard to sleep disturbance. The data shown for the 24 hour patch also accorded with the balance of the evidence in that patch users experienced statistically significantly more sleep disturbance than those on placebo. The Panel considered, however, that placed side by side, the bar charts implied that while Nicorette 16 hour Patch resulted in 3.4-5.4% sleep disturbance, the incidence with the 24 hour patch was 20.4-26% and that these figures were directly comparable; that was not so. The Panel further noted that sleep disturbance on placebo for the Nicorette studies had ranged from 4.0%-5.9% whilst in the 24 hour patch studies the comparable figures had ranged from 7.5-16%. The Panel considered that the footnote 'Source: Data set used for the Cochrane review meta-analysis – a comprehensive overview, representative of the body of evidence for NRT use' which ran beneath both bar charts strengthened the impression that the data could be directly compared; reference to the Cochrane review gave the impression that it was valid to do so. The Panel thus considered that the presentation of the data was misleading as alleged. A breach of the Code was ruled.

The Panel noted that although the bar charts referred to sleep disturbance, only the insomnia data were shown. The results for vivid dreams/nightmares had not been included. The Panel considered that sleep disturbance was a broad term which encompassed more than insomnia. The Panel considered that the bar charts were thus misleading and did not give a fair and balanced view of sleep disturbance and nicotine patches. A breach of the Code was ruled.

GlaxoSmithKline Consumer Healthcare noted the claim 'Nocturnal nicotine dosing is proven to exacerbate sleep disturbance – a recognised symptom of nicotine withdrawal' appeared immediately below the two bar charts considered above. GlaxoSmithKline Consumer Healthcare alleged that the claim was misleading as 24 hour dosing did not make the symptoms of nicotine withdrawal worse. By definition patients who suffered sleep disturbance as part of their withdrawal symptoms would be improved by administration of nicotine (otherwise it would not be classified as a withdrawal symptom). The way this claim was written led the reader to believe that all types of sleep disturbance would be increased with overnight nicotine administration.

The Panel considered that the claim was misleading as it did not distinguish between sleep disturbance caused by nicotine withdrawal and the sleep disturbance caused by nocturnal nicotine. A breach of the Code was ruled.

GlaxoSmithKline Consumer Healthcare noted that the claim 'With Nicorette 16 hour Patch patients are twice as likely to succeed whilst minimising the risk of sleep disturbance' appeared, printed in white on a red block, in the bottom left hand corner of the leavepiece. GlaxoSmithKline Consumer Healthcare alleged that the claim was misleading as it was a hanging comparison. Whilst Nicorette might be twice as likely to succeed as placebo, the risk of sleep disturbance was not minimised compared to placebo, and the probability of success was not superior to 24 hour patch therapy.

The Panel noted that the claim had appeared on a leavepiece which had compared Nicorette with placebo in terms of sleep disturbance and which had also implied a comparison in that regard with a 24 hour patch. Given the context in which the claim 'With Nicorette 16 hour Patch patients are twice as likely to succeed whilst minimising the risk of sleep disturbance' appeared it was thus unclear with what Nicorette was being compared – placebo or 24 hour patch. The Panel thus considered that the claim was a hanging comparative and ruled a breach of the Code.

GlaxoSmithKline Consumer Healthcare complained about the promotion of Nicorette Patches (transdermal nicotine) by Pfizer Consumer Healthcare. The items at issue were an advertisement (ref PF020/12/17) and a leavepiece (ref PF001/09/03).

Nicorette Patches contained nicotine, 5mg, 10mg or 15mg, released over 16 hours' use. GlaxoSmithKline Consumer Healthcare marketed NiQuitin CQ Patches (transdermal nicotine) which delivered 7mg, 14mg or 21mg nicotine over 24 hours.

* * * * *

The Panel noted that throughout its complaint GlaxoSmithKline had only alleged breaches of Clause 7 of the Code. In its consideration of the case the Panel made rulings of those sub-clauses of Clause 7 which most closely matched the wording of the complaint.

* * * * *

A Advertisement

1 Headline 'Your patients don't smoke while they sleep, so why treat them as if they do?'

COMPLAINT

GlaxoSmithKline Consumer Healthcare stated that the headline, which set the tone for the advertisement, was a valid question, but as Pfizer Consumer Healthcare made no effort to answer it the reader was left with the impression that there was no reason to give overnight nicotine. This was not a balanced, fair or objective evaluation of the evidence. In intercompany correspondence Pfizer Consumer Healthcare stated that this was 'a rhetorical question designed to raise the issue of sleep disturbance during smoking cessation and to lead the reader on to the copy text which elaborates further. The purpose of the advertisement is to highlight the benefits of 16 hour patch use in the context of exacerbation of sleep disturbance…'.

GlaxoSmithKline Consumer Healthcare noted that a rhetorical question did not seek an answer but served to impress the reader that the answer was so obvious as to not need an explanation. There were legitimate reasons to give nicotine overnight in a 24 hour patch, which were not mentioned, thus making the advertisement unbalanced and misleading. GlaxoSmithKline Consumer Healthcare noted that the summary of product characteristics (SPC) for NiQuitin CQ stated 'Patches may be removed before going to bed if desired. However use for 24 hours is recommended to optimise the effect against morning cravings'. This clinical benefit should be made apparent to the readers who otherwise might be hoodwinked to believe that there was no reason to administer nicotine overnight. A breach of Clause 7 was alleged.

RESPONSE

Pfizer Consumer Healthcare stated that it struggled to see the issue. It was an incontrovertible fact that smokers did not smoke whilst they were asleep and the rest of the headline was designed to provoke thought amongst health professionals. The question was qualified in the copy which stated 'Nicorette 16 hour Patch is uniquely designed to deliver a full dose of nicotine only during normal waking hours'. This was again incontrovertible – the smoker smoked during waking hours thus getting their nicotine 'fix' and the Nicorette 16 hour patch replaced smoking by delivering nicotine during those same waking hours.

Pfizer Consumer Healthcare noted that the Collins English Dictionary defined a rhetorical question as 'a question to which no answer is required: used especially for dramatic effect'. This was precisely the desired effect here; to cause the reader to pause for thought. The copy then went on to explain the adverse consequence of dosing with nicotine at night (see also point 2 of the complaint below) ie unnecessary sleep disturbance.

Pfizer Consumer Healthcare noted GlaxoSmithKline Consumer Healthcare's contention regarding a clinical benefit for the use of the 24 hour patch in optimising any effect against morning cravings. Pfizer Consumer Healthcare noted however that it made no claim with respect to morning cravings and so the complaint was irrelevant. Secondly, the Cochrane systematic review of nicotine replacement therapy (NRT) showed no evidence of a difference in clinical effectiveness between 16 and 24 hour patches which suggested no clinical benefit overall of a 24 hour patch vs a 16 hour patch.

Pfizer Consumer Healthcare denied that this was a breach of Clause 7 of the Code.

PANEL RULING

The Panel noted that Nicorette Patches were to be applied on waking (usually in the morning) and removed 16 hours later (usually at bedtime). Thus while patients slept they did not receive any transdermal nicotine. NiQuitin Patches, however, were to be applied once a day, at the same time each day and worn continuously for 24 hours. The NiQuitin CQ Patch SPC stated that the patches could be removed before going to bed if desired but use for 24 hours was recommended to optimise the effect against morning cravings.

The Panel considered that, the headline 'Your patients don't smoke while they sleep, so why treat them as if they do?' drew attention to the use of 16 hour as opposed to 24 hour patches. The advertisement was designed to promote Nicorette Patches and in doing so referred to one of the differences between Nicorette Patches and NiQuitin CQ Patches. The Panel did not consider that not answering the rhetorical question meant that the headline was either unbalanced or misleading as alleged. No breach of Clause 7.2 was ruled.

2 Claim 'Which helps your patients avoid the nocturnal nicotine dosing commonly associated with unnecessary sleep disturbance'

This claim appeared in the main body of the text and was immediately preceded by 'Nicorette 16 hour Patch is uniquely designed to deliver a full dose of nicotine only during normal waking hours'. The claim was asterisked to a footnote which read 'Nicorette 16 hour Patch is the only one not shown to cause sleep disturbance over and above placebo levels'.

COMPLAINT

GlaxoSmithKline Consumer Healthcare noted that sleep disturbance claims had been the subject of

rulings in Case AUTH/1329/6/02 where a breach was ruled and in Case AUTH/1380/10/02 where no breach was ruled. In Case AUTH/1380/10/02 although no breach of undertaking was found as the material at issue was sufficiently different from that at issue in Case AUTH/1329/6/02, the Panel specifically requested 'that Pharmacia be advised of its concerns' one of which was 'whether the material was sufficiently clear regarding the sleep disturbance caused by withdrawal of nicotine' thus inviting Pharmacia (now Pfizer) to make this clear in any future material to avoid subsequent breaches of the Code. It did not give Pfizer Consumer Healthcare carte blanche to discuss sleep disturbance in an unbalanced way.

GlaxoSmithKline Consumer Healthcare alleged that the claim 'Which helps your patients avoid the nocturnal nicotine dosing commonly associated with unnecessary sleep disturbance' was in an advertisement that gave an unbalanced view of sleep disturbance during smoking cessation. The visual was of a woman sleeping peacefully, inviting the reader to assume a good night's sleep on Nicorette patch. The text did not overtly mention sleep disturbance caused by nicotine withdrawal, it simply mentioned 'unnecessary' sleep disturbance and in a footnote claimed 'Nicorette 16 hour patch is the only one not shown to cause sleep disturbance over and above placebo levels'. The advertisement did not make it sufficiently clear that sleep disturbance commonly occurred when quitting smoking, as it was one of the recognised symptoms of nicotine withdrawal, and that Nicorette 16 hour patch did not enable patients to avoid this sleep disturbance caused by nicotine withdrawal. Neither did it mention any of the studies showing an improvement or no change in sleep disturbance during smoking cessation when overnight nicotine was administered (Wetter *et al* 1995; Wolter *et al* 1996). In focussing solely on sleep disturbance, this campaign gave an unbalanced view of nicotine patches, raising undue concern about 24 hour patch safety. GlaxoSmithKline Consumer Healthcare recognised that sleep disturbance could occur in patients quitting smoking and in those using 24 hour patch therapy. However, studies had shown that the vast majority of these reports were not severe, and very rarely led to discontinuation or change of therapy. Both the Cochrane review and the National Institute of Clinical Excellence (NICE) recognised local side effects, such as skin rashes, rather than sleep disturbance to be the most troublesome; 'The only side effect which appears to interfere with use of the patch is skin sensitivity and irritation;…' (Cochrane) and 'The most common side effects are localised reactions (for example, skin irritation with patches, irritation of the nose, throat and eyes with nasal spray), but minor sleep disturbances occur commonly. These side effects are unlikely to lead to discontinuation of therapy' (NICE). Also, the claim referred to 'your patients' who, by definition, must be smokers. The study cited in support of the claim (Davila *et al* 1994) was in non-smokers, who were not tolerant to the effects of nicotine and whose results could not be extrapolated to a population of smokers attempting to quit. GlaxoSmithKline Consumer Healthcare alleged breaches of Clause 7.

RESPONSE

Pfizer Consumer Healthcare noted that it had previously used the claim '… avoids the nocturnal nicotine dosing often associated with sleep disturbance'. This was the subject of Case AUTH/1380/10/02 in which the Panel did not rule a breach of the Code but ruled that the material at issue referred to minimising the risk of unnecessary sleep disturbance. The Panel queried whether the material was sufficiently clear regarding the sleep disturbance caused by the withdrawal of nicotine, a point which had now been noted by GlaxoSmithKline Consumer Healthcare in this complaint.

In order to address the concerns of the Panel and to avoid any further misinterpretation, Pfizer Consumer Healthcare now specifically included the word 'unnecessary' to distinguish between the sleep disturbance which was part and parcel of quitting and the additional disruption to sleep caused by nocturnal nicotine dosing. The company considered that the meaning was clear.

Pfizer Consumer Healthcare noted that the NiQuitin Patch SPC stated that abnormal dreams and insomnia were systemic effects found in clinical studies which were not included as undesirable effects in the Nicorette SPC and that the NiQuitin SPC continued to advise that patches might be removed before going to bed if desired. Furthermore, in the US, the prescribing information for Nicoderm CQ (the US name for NiQuitin) was more explicit than the SPC stating: 'If you have vivid dreams or other sleep disturbances, you may remove the patch at bedtime and apply a new one in the morning'. It was clear that GlaxoSmithKline Consumer Healthcare understood that 24 hour nicotine dosing was associated with sleep disturbance beyond that attributable to quitting.

The advertisement at issue showed a woman sleeping which reinforced the headline that whilst she was asleep, she was not smoking. The greatest impact from the advertisement would be the headline and the visual which were linked. No further inference was intended and Pfizer Consumer Healthcare disagreed that this gave an unbalanced view of sleep disturbance during smoking cessation and questioned whether it was possible that those rather closer to the therapeutic area than the target health professional might be reading too much into the visual.

Pfizer Consumer Healthcare noted the complainant's objection to the footnote 'Nicorette 16 hour Patch is the only one not shown to cause sleep disturbance over and above placebo levels' because the text did not make it sufficiently clear that sleep disturbance commonly occurred when quitting smoking. The meaning of the footnote would be quite clear to the health professional: that sleep disturbance was observed in placebo treated patients ie those withdrawing from cigarettes without NRT and that the 16 hour patch was the only NRT patch which had not been shown to exacerbate this effect. Pfizer Consumer Healthcare stated that it did not claim to avoid the sleep disturbance caused by withdrawing from cigarettes, but contended that Nicorette would not make this worse. This was supported by the cited references (Davila *et al*; Imperial

Cancer Research Fund (ICRF) General Practice Research Group 1993; Russell *et al* 1993).

Pfizer Consumer Healthcare did not agree that in focussing solely on sleep disturbance this campaign gave an unbalanced view of nicotine patches, raising undue concern about 24 hour patch safety. The issue was one of choice, offering health professionals the chance to reflect on what they chose to prescribe and why. There was no claim about the comparative safety profiles of 16 hour and 24 hour patches. Pfizer Consumer Healthcare considered, however, that the potential for additional sleep disturbance through nocturnal nicotine dosing, in addition to that caused by quitting itself to be an important consideration for the health professional when advising patients.

GlaxoSmithKline Consumer Healthcare's references to the Cochrane and NICE reviews were therefore redundant but as a point of correction, Cochrane did not assess side effects and NICE acknowledged sleep disturbance whilst also stating that side effects were unlikely to lead to discontinuation of therapy. This in itself was an interesting point as Pfizer Consumer Healthcare made no claim about discontinuation of therapy which GlaxoSmithKline Consumer Healthcare appeared to be parcelling up with sleep disturbance. The two were completely separate issues. It was of course true that patients who had sleep disturbance might consider their quality of life or well-being to be affected, in which case a patch which helped them to 'avoid the nocturnal nicotine dosing commonly associated with unnecessary sleep disturbance' might be highly relevant.

Pfizer Consumer Healthcare acknowledged that Davila *et al* was conducted in non-smokers and that its findings might not necessarily extrapolate to smokers. However, the link between nocturnal nicotine dosing and sleep disturbance in smokers was well established in studies using 24 hour nicotine patch. The ICRF study in 1686 heavy smokers aged 25-64 with a mean cigarette consumption of 24/day and a mean duration of smoking of 25 years, demonstrated that sleep disturbance was the most common event and was nearly three times as frequent in the 24 hour patch group as in the placebo group (20.4% vs 7.5%; $p<0.0001$).

GlaxoSmithKline Consumer Healthcare cited Wetter *et al* and Wolter *et al* as showing an improvement or no change in sleep disturbance when overnight nicotine was administered. These studies used highly specialised objective assessments of the sleep architecture and comment on various parameters which might or might not be affected by quitting and/or 24 hour NRT. It would be unclear to the general health professional reader who would not be a specialist in sleep architecture whether or not the individual elements which comprised the total sleep experience were impacted positively or negatively in these studies. The individual's perception of their night's sleep was also not considered. Pfizer Consumer Healthcare noted again that abnormal dreams and insomnia were listed on the NiQuitin 24 hour Patch SPC and not the Nicorette 16 hour Patch SPC.

The fact remained that nocturnal nicotine dosing caused sleep disturbance over and above that caused by quitting itself, which might be an important consideration for some individuals: back to the issue of choice. It was for these reasons that Pfizer Consumer Healthcare submitted that this was not a breach of Clause 7 of the Code.

PANEL RULING

The Panel noted that smokers who stopped smoking were likely to experience sleep disturbance due to withdrawal from nicotine. Studies had shown no change to such sleep disturbance with Nicorette Patches; the claim in question was asterisked to a footnote which stated 'Nicorette 16 hour Patch is the only one not shown to cause sleep disturbance over and above placebo levels'. Sleep disturbance was not listed in the Nicorette Patch SPC as an undesirable effect of therapy. Conversely the Panel noted GlaxoSmithKline Consumer Healthcare's submission that sleep disturbance could occur in those using 24 hour patch therapy. Insomnia (12.3%) and abnormal dreams (17.3%) were listed in the NiQuitin Patch SPC as possible side effects of therapy, both of which occurred more frequently than with placebo. It was stated in the SPC that NiQuitin patches could be removed before going to bed if required. The Panel considered that there were clear differences between Nicorette Patches and NiQuitin Patches in terms of their propensity to add to the sleep disturbance which occurred as a consequence of nicotine withdrawal. The Panel did not consider that focussing on sleep disturbance gave an unbalanced view of nicotine patches or raised undue concern about the safety of 24 hour patches as alleged. No breach of Clauses 7.2 and 7.9 was ruled.

The Panel noted Pfizer Consumer Healthcare's submission that in the claim '[Nicorette] helps your patients avoid the nocturnal nicotine dosing commonly associated with unnecessary sleep disturbance' the word 'unnecessary' was included to distinguish between the sleep disturbance which was part and parcel of quitting and the additional disruption to sleep caused by nocturnal nicotine dosing. The Panel, however, did not consider that the claim adequately distinguished between the two types of sleep disturbance and considered that some readers would be left with the impression that those taking Nicorette would not have a disturbed night's sleep which was not necessarily so as they would continue to experience the sleep disruption caused by nicotine withdrawal. The footnote 'Nicorette 16 hour Patch is the only one not shown to cause sleep disturbance over and above placebo levels' did not negate the impression given. The expectation of a good night's sleep on Nicorette was strengthened by the visual of a woman sleeping peacefully in bed. On balance the Panel considered that the claim was misleading. A breach of Clause 7.2 was ruled.

3 Claim '… Nicorette 16 hour Patch also provides maximum craving control when patients are at their most vulnerable'

COMPLAINT

GlaxoSmithKline Consumer Healthcare alleged that the claim was misleading because it could be interpreted in a number of ways.

The claim was referenced to four studies (Brandon *et al* 1986; Shiffman *et al* 1996; Ussher and West 2003 and Johansson *et al* 1996), three of which discussed the timing of relapses, one of which was in 16 hour patch users. The 16 hour patch study (Ussher and West) did not show a preferential reduction of lapses in the afternoons for patients using a 16 hour patch compared to those on placebo, as would be expected from this claim. Johansson *et al* was a pharmacokinetic study showing peak nicotine levels 6-8 hours after application. The study did not investigate craving control throughout the day. As there was no level where it was accepted that craving control occurred, a pharmacokinetic profile that provided greater nicotine levels later in the day than in the morning did not support the clinical claim 'provides maximum craving control when patients are at their most vulnerable'. Further, the NiQuitin CQ patch delivered higher nicotine levels than Nicorette throughout the whole day as reported in a direct head-to-head study (Fant *et al* 2000) so even if there were a direct correlation between nicotine levels and craving control, NiQuitin CQ would provide 'even more maximum craving control'. Clearly, the data quoted did not support the claim that Nicorette patch provided maximum craving control. In fact, in the only head-to-head clinical study comparing Nicorette patch with NiQuitin CQ patch (Shiffman *et al* 2000) in patients who had their worst cravings in the morning, NiQuitin CQ achieved greater craving control during all intervals and all time blocks throughout the day, thus including 'when patients are at their most vulnerable'.

GlaxoSmithKline Consumer Healthcare considered that two aspects to this claim needed further clarification; firstly, Nicorette 16 hour patch did not provide 'maximum craving control'. Maximum craving control could easily be achieved by having a cigarette and completely relieving the craving. In intercompany correspondence, Pfizer Consumer Healthcare defined 'maximum' in terms of 'The time or period during which the highest point or degree is attained', rather than the amount of craving relief obtained. No data had been provided showing the level of craving control achieved throughout the day at various points to substantiate the claim. The second aspect was 'when patients are at their most vulnerable'. Most vulnerable to what? Cravings? Relapse? The two were not interchangeable and smokers did not necessarily relapse at a time when cravings were at their peak. In intercompany correspondence, Pfizer Consumer Healthcare appeared to be confusing cravings with relapse. The claim referred to 'maximum craving control when patients are at their most vulnerable'. Many patients were most vulnerable to cravings first thing in the morning when the Nicorette patch left a gap in protection (see Case AUTH/1401/12/02) and using Pfizer Consumer Healthcare's own pharmacokinetic profile rationale could not possibly provide 'maximum craving control' as nicotine levels were low. As morning craving was a predictor of relapse, even afternoon relapse, part of the solution might lie in the treatment of morning craving (Shiffman *et al* 1997). GlaxoSmithKline Consumer Healthcare agreed that patients might well be more vulnerable to relapse in the afternoon or evening, as there was more opportunity for lapsing, with exposure to others smoking, alcohol, and release from smoking restricted environments. However, Pfizer Consumer Healthcare had not provided data that Nicorette prevented relapse in the afternoon relative to placebo. Breaches of Clause 7 were alleged.

RESPONSE

Pfizer Consumer Healthcare stated that the claim should be read in the context of the full sentence ie 'And by mimicking your patient's daily smoking pattern, Nicorette 16 hour Patch also provided maximum craving control when patients are at their most vulnerable'.

Pfizer Consumer Healthcare noted GlaxoSmithKline Consumer Healthcare's comment that NiQuitin CQ patch delivered higher nicotine levels throughout the whole day and would therefore provide 'even more maximum craving control'. That was an interesting claim of little relevance as once the 'maximum' required had been achieved more was unnecessary. This was backed by the findings of the Cochrane systematic review: which showed no evidence of a difference in clinical effectiveness between 16 and 24 hour patches.

Pfizer Consumer Healthcare also noted that GlaxoSmithKline Consumer Healthcare had stated that having a cigarette would provide maximum craving control. Of course it would: but this advertisement was aimed at health professionals trying to advise quitters, not smokers. Successful quitters could not simply light up!

Shiffman (1996) and Ussher and West showed that the late afternoon/evening was a time of vulnerability for temptation to lapse. Ussher and West confirmed that 100% of failed quitters relapsed during the day not at night ie 7% relapsed between 6am-noon, 43% relapsed in the afternoon and 50% relapsed in the evening. Nicorette 16 hour patch provided nicotine replacement which covered this period of vulnerability as confirmed by Johansson *et al*. This was the meaning of the claim.

Pfizer Consumer Healthcare noted that it was only referring to the time of day when patients who were trying to quit were at their most vulnerable to relapse (afternoon and evening), a time with which GlaxoSmithKline Consumer Healthcare agreed in its complaint.

In summary both companies seemed to agree that smokers trying to quit were most vulnerable to relapse in the afternoon/early evening. GlaxoSmithKline Consumer Healthcare noted in its complaint that morning cravings were a predictor to relapse, but previously stated that cravings and relapse were not interchangeable. There appeared to be an element of contradiction in its argument.

Pfizer Consumer Healthcare stated that whilst it denied a breach of Clause 7, it proposed, in order to resolve the matter, to revise the claim accordingly in future promotional materials.

PANEL RULING

The Panel considered that it was not clear whether the claim '… Nicorette 16 hour Patch also provides maximum craving control when patients are at their most vulnerable' meant that Nicorette patches controlled cravings when they were at their worst ie in the morning, or controlled them when smokers were most vulnerable to relapsing ie afternoon/evening. Pfizer Consumer Healthcare had submitted that it was the latter. The Panel considered that the claim was ambiguous and misleading as alleged. A breach of Clause 7.2 was ruled.

The Panel noted that Pfizer Consumer Healthcare, although denying a breach of the Code, proposed to revise the claim.

B Leavepiece (ref PF001/09/03)

The leavepiece was entitled 'Nicorette Patch – specially designed for waking hours only' and featured two bar charts, one depicting incidence of sleep disturbance for Nicorette from two studies, Tønnesen *et al* (1999) and Sachs *et al* (1993), and the other depicting the incidence of sleep disturbance with a 24 hour patch ie NiQuitin, from two studies, ICRF General Practice Research Group and Richmond *et al* 1994. Sleep disturbance with Nicorette was shown to be similar to that of placebo (p=ns) at 5.4% in one study and 3.5% in the other. The incidence of sleep disturbance for the 24 hour patch was statistically significantly greater than placebo with 20.4% ($p<0.0001$) in one study and 26% ($p<0.03$) in the other.

GlaxoSmithKline Consumer Healthcare submitted that using the risk of sleep disturbance as the main promotional platform gave unwarranted clinical significance to this side effect. Most patients using a 24 hour patch would not suffer sleep disturbance. As discussed above (point A2), even if they did it was very unlikely to warrant a change of therapy or discontinuation as the vast majority of sufferers reported their sleep disturbance as mild or moderate. Further, for a proportion of patients, sleep disturbance would be alleviated by using nicotine overnight.

1 Presentation of the two bar charts

COMPLAINT

GlaxoSmithKline Consumer Healthcare stated that the use of two bar charts side by side invited comparison when none could be made due to differences in the study conditions and data collection. The footnote 'Cochrane review meta-analysis – a comprehensive overview, representative of the body of evidence for NRT use' under the bar charts was misleading. The Cochrane analysis specifically stated 'No attempt was made in this overview to synthesise quantitatively the incidence of the various side effects reported with the different NRT preparations. This was because of the extensive variation in reporting the nature, timing and duration of symptoms' and 'The only side effect which appears to interfere with use of the patch is skin sensitivity and irritation; this may affect up to 54% of patch users, but it is usually mild and rarely leads to withdrawal of patch use', thus confirming the lack of clinical importance of sleep disturbance. Reference to the Cochrane meta-analysis lent undue weight and credence to the leavepiece; the reader would be falsely reassured that the Cochrane meta-analysis supported this interpretation, when in fact Cochrane specifically indicated that it was inappropriate to compare the incidence of side effects due to inter-study variation.

The data quoted for Tønnesen *et al* were incorrect; n=3575 included patients from all 5 arms in the study, three of which were not consistent with the licensed particulars of Nicorette patch. Although 'insomnia' was quoted in the paper as 5.9% v 5.4%, the bar chart axis and remainder of the promotional piece referred to 'sleep disturbance'. In this study, nightmares were reported in 7% (15mg) v 6% for placebo, and vivid dreams were 18% v 15%. Both of these conditions were examples of sleep disturbance. The incorrect reference to 'sleep disturbance' provided a falsely low figure which was misleading. Breaches of Clause 7 were alleged.

GlaxoSmithKline Consumer Healthcare noted that Pfizer Consumer Healthcare had agreed not to refer to Cochrane 'to avoid any potential for confusion', but did not agree that its use lent undue credence to the item.

The incorrect labelling of the bar chart axis in Tønnesen *et al* was not negated by a similar incorrect labelling for one of the other bar charts. The complaint was that it was misleading to label a bar chart 'sleep disturbance' when the incidence depicted was insomnia, which was only one type of sleep disturbance. It must be reiterated that comparisons of side effect reporting across these studies could not be made due to extensive differences in data collection procedures.

RESPONSE

Pfizer Consumer Healthcare stated the bar charts at issue were designed to depict data for both the 16 hour and 24 hour patches. They were not intended to be directly comparable and for this reason they were distinct from each other. By separating the bar charts the company had ensured that there was no suggestion that they were from the same trial. Furthermore, each bar had been clearly labelled with the study name and the number of patients. Representative studies involving large numbers of patients had been selected.

The footnote under the bar charts read: 'SOURCE: Data set used for the Cochrane review meta-analysis – a comprehensive overview, representative of the body of evidence for NRT use'.

The reference to Cochrane was to clarify the selection of the trials quoted (Tønnesen *et al*, Sachs *et al*, ICRF General Practice Research Group and Richmond *et al*). A review of the patch studies described in Cochrane revealed that these studies specifically discussed sleep disturbance as a side effect of therapy and included significant numbers of patients. Pfizer Consumer Healthcare did not agree that the reference to Cochrane lent undue weight and credence to the

leavepiece as suggested. However, to avoid any potential for confusion the company had agreed not to use this statement in any future advertising.

Pfizer Consumer Healthcare noted GlaxoSmithKline Consumer Healthcare's contention that the number of patients in Tønnesen *et al* had been incorrectly quoted. Pfizer Consumer Healthcare noted that it had included all 5 arms of the study. The company continued to maintain that it was common practice where quoting study numbers to include the total number of individuals in the study, rather than 'cherry picking'. Sleep disturbance was not reported for each individual arm within the study and therefore it was necessary to quote the final value for the entire study population. Clearly, it would be expected that by including data utilising higher doses and longer duration of usage, any effect on the sleep disturbance incidence would be skewed against the 15mg patch.

For consistency, where insomnia data was available it had been quoted. Therefore although data relating to nightmares and vivid dreams were available in Tønnesen *et al*, the insomnia data had been quoted. The same principle had been applied to Richmond *et al* for the 24 hour patch. In fact the available data for vivid dreams/nightmares demonstrated a comparable incidence to placebo for the 16 hour patch trials (Tønnesen *et al*: nightmares 7% vs 6%, vivid dreams 18% vs 15% for active vs placebo respectively; Sachs: abnormal/vivid dreams or nightmares 0% for active and placebo). In contrast Richmond *et al* using the 24 hour patch showed an incidence of vivid dreams of 30% in the active group compared with 6% in the placebo group.

For these reasons, therefore, Pfizer Consumer Healthcare did not agree that it had breached Clause 7.

PANEL RULING

The Panel noted its comments above at point A2 with regard to the differences in sleep disturbance with the 16 hour and 24 hour patches. The Panel further noted GlaxoSmithKline Consumer Healthcare's submissions that sleep disturbance was unlikely to lead to a change in therapy and that it lacked clinical importance. Nonetheless the Panel considered that it was not unreasonable to draw attention to sleep disturbance and the difference between the two patches given that some patients might find even mild sleep disturbance annoying.

The Panel noted that data from Tønnesen *et al*, which was included in the bar chart depicting sleep disturbance with Nicorette, appeared to relate to the whole study population ie n=3,575. The study had included five treatment arms two of which (n=1,430) had used high-dose Nicorette (25mg) over 16 hours, two of which (n=1,431) had used standard dose Nicorette (15mg) over 16 hours and one of which (n=714) had used placebo. The authors had reported that the incidence of insomnia was 4.9%, 5.4%, and 5.9% in the 25mg, 15mg, and placebo groups respectively. The bar chart showed the figures of 5.4% and 5.9% for Nicorette and placebo respectively and so in that regard the data did not relate to the whole study population but only to those using either 15mg patches or placebo (n=2,145). It was thus inaccurate and misleading to label the chart n=3,575. The Panel ruled a breach of Clause 7.2 of the Code.

The Panel considered that the presentation of the two bar charts invited comparison of the results contained therein. The data shown for the Nicorette 16 hour patch accorded with the balance of the evidence in so much as there was no significant difference between active and placebo with regard to sleep disturbance. The data shown for the 24 hour patch also accorded with the balance of the evidence in that patch users experienced statistically significantly more sleep disturbance than those on placebo. The Panel considered, however, that placed side by side, the bar charts implied that while Nicorette 16 hour Patch resulted in 3.4-5.4% sleep disturbance, the incidence with the 24 hour patch was 20.4-26% and that these figures were directly comparable; that was not so. The Panel further noted that sleep disturbance on placebo for the Nicorette studies had ranged from 4.0%-5.9% whilst in the 24 hour patch studies the comparable figures had ranged from 7.5-16%. The Panel considered that the footnote 'Source: Data set used for the Cochrane review meta-analysis – a comprehensive overview, representative of the body of evidence for NRT use' which ran beneath both bar charts strengthened the impression that the data could be directly compared; reference to the Cochrane review gave the impression that it was valid to do so. The Panel thus considered that the presentation of the data was misleading as alleged. Breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that although the bar charts referred to sleep disturbance, only the insomnia data were shown. The results for vivid dreams/nightmares had not been included. The Panel considered that sleep disturbance was a broad term which encompassed more than insomnia. The Panel considered that the bar charts were thus misleading and did not give a fair and balanced view of sleep disturbance and nicotine patches. A breach of Clause 7.8 was ruled.

2 Claim 'Nocturnal nicotine dosing is proven to exacerbate sleep disturbance – a recognised symptom of nicotine withdrawal'

This claim appeared immediately below the two bar charts considered in point B1 above.

COMPLAINT

GlaxoSmithKline Consumer Healthcare alleged that the claim was misleading as 24 hour dosing did not make the symptoms of nicotine withdrawal worse. By definition patients who suffered sleep disturbance as part of their withdrawal symptoms would be improved by administration of nicotine (otherwise it would not be classified as a withdrawal symptom). The way this claim was written led the reader to believe that all types of sleep disturbance would be increased with overnight nicotine administration. Breaches of Clause 7 were alleged.

GlaxoSmithKline Consumer Healthcare stated that it was the linking of two statements that made this

claim misleading. However, in Case AUTH/1380/10/02 the Panel had requested 'that Pharmacia be advised of its concerns' one of which was 'whether the material was sufficiently clear regarding the sleep disturbance caused by withdrawal of nicotine' thus inviting Pharmacia (now Pfizer) to make this clear in any future material to avoid subsequent breaches of the Code. Whilst there were data to suggest that sleep disturbance might occur more frequently with nocturnal nicotine dosing than placebo, sleep disturbance was also a feature of nicotine withdrawal. In the first situation sleep disturbance was due to the presence of nicotine and on the other it was due to its absence. The way this statement was written drew no distinction between these two situations and suggested that the nocturnal nicotine exacerbated sleep disturbance due to nicotine withdrawal which was clearly misleading.

RESPONSE

Pfizer Consumer Healthcare stated that after further review it now appreciated that the statement could be misleading as it confused the two distinct forms of sleep disturbance and agreed not to use this statement in future promotional items. The company apologised for an inadvertent breach of Clause 7 in this regard.

PANEL RULING

The Panel considered that the claim was misleading as it did not distinguish between sleep disturbance caused by nicotine withdrawal and the sleep disturbance caused by nocturnal nicotine. A breach of Clause 7.2 was ruled. The Panel noted that Pfizer Consumer Healthcare had accepted that the claim was misleading and had agreed not to use it again.

3 Claim 'With Nicorette 16 hour Patch patients are twice as likely to succeed whilst minimising the risk of sleep disturbance'

This claim appeared, printed in white on a red block, in the bottom left hand corner of the leavepiece.

COMPLAINT

GlaxoSmithKline Consumer Healthcare alleged that the claim was misleading as it was a hanging comparison. Whilst Nicorette might be twice as likely to succeed as placebo, the risk of sleep disturbance was not minimised compared to placebo, and the probability of success was not superior to 24 hour patch therapy. Breaches of Clause 7 were alleged.

RESPONSE

Pfizer Consumer Healthcare stated that 'Twice as likely to succeed' had become part of the smoking cessation vocabulary, and referred to the clearly referenced findings of the Cochrane review, that a quitter was twice as likely to succeed if NRT was used. Pfizer Consumer Healthcare believed GlaxoSmithKline Consumer Healthcare had used something similar itself.

The claim was a simple contraction of two statements of fact, which were shown individually and referenced appropriately on the leavepiece ie 'Nicorette 16 hour patch has not been shown to cause sleep disturbance over placebo levels' and 'Patients are twice as likely to succeed over willpower alone'.

Pfizer Consumer Healthcare noted that Cochrane stated that NRT users were twice as likely to succeed compared to placebo – which applied to Nicorette as a form of NRT – and the case had already been made that Nicorette did not increase sleep disturbance over placebo levels.

Pfizer Consumer Healthcare therefore denied a breach of Clause 7.

PANEL RULING

The Panel noted that the claim had appeared on a leavepiece which had compared Nicorette with placebo in terms of sleep disturbance and which had also implied a comparison in that regard with a 24 hour patch. Given the context in which the claim 'With Nicorette 16 hour Patch patients are twice as likely to succeed whilst minimising the risk of sleep disturbance' appeared it was thus unclear with what Nicorette was being compared – placebo or 24 hour patch. The Panel thus considered that the claim was a hanging comparative and ruled a breach of Clause 7.2 of the Code.

Complaint received **17 March 2004**

Case completed **11 May 2004**

NHS TRUST CHIEF EXECUTIVE AND CONSULTANT PHYSICIAN v ABBOTT LABORATORIES

Supply of Humira

The chief executive of an NHS Trust and a consultant physician complained about the free supply of Humira (adalimumab) on compassionate grounds by Abbott Laboratories prior to the product being granted a marketing authorization. The complainants were concerned about the financial impact of this activity.

The complainants explained that the trust in which they worked had inherited a significant financial liability following the licensing of Humira after it had previously been provided free of charge to one of its rheumatologists.

The complainants noted that in this particular case, the trust had been informed that Humira was made available, prior to licensing, to patients within the trust on compassionate grounds. The complainants stated that the rationale for this compassionate provision was said to be the scarcity of the subcutaneous competitor, Enbrel (etanercept) and/or the inconvenience of travelling to the rheumatology centre for intravenous Remicade (infliximab). Both Enbrel and Remicade were licensed products.

The complainants stated that there were serious reasons to question this rationale. Firstly, both Enbrel and Remicade were funded for use and recommended by the National Institute for Clinical Excellence (NICE) whereas Humira was not funded, recommended or licensed. Secondly, the majority of patients offered Humira came from one geographical area served by one rheumatologist. Thirdly, patients under the care of the trust received Enbrel during this period. Finally, numerous patients from around the region were able to travel in to the rheumatology centre for Remicade treatment.

The complainants stated that as soon as Humira was licensed, Abbott immediately threatened the free supplies to those patients treated on compassionate grounds.

The Panel noted that it was not unacceptable for companies to provide medicines on a compassionate basis to patients who had participated in clinical trials and/or those who might benefit from treatment before the medicine was licensed and became commercially available. The Panel noted that such medicines must not be promoted prior to the grant of the marketing authorization.

The Panel considered that the arrangements for the supply of unlicensed medicines on a named patient basis were potentially subject to the Code.

The Panel noted that whilst the complaints referred to the supply of Humira on a named patient basis to one unidentified rheumatologist, Abbott stated that it had supplied the product to two rheumatologists within the trust.

The Panel examined the arrangements for the supply of Humira. Abbott submitted that requests resulted from intolerance, lack of efficacy or inappropriateness of licensed alternative treatments based on clinical judgement or non-availability. The Panel noted that the MCA (Medicines Control Agency; now known as the Medicines and Healthcare products Regulatory Agency) Guidance Note No.14 – The supply of unlicensed relevant medicinal products for individual patients – stated that responsibility for deciding whether an individual patient had 'special needs' which the licensed product could not meet should be a matter for the doctor responsible for the patient's care. This responsibility was reflected in the letter of agreement between Abbott and the requesting physician. The Panel noted the complainants' submission that patients under the care of the trust received Enbrel or travelled to a rheumatology centre for Remicade treatment during the relevant period. The Panel noted that the majority of the requests for compassionate supplies of Humira within the trust came from one physician who requested supplies for 27 patients.

The letter of agreement between Abbott and the requesting physician set out the conditions of named patient supply including the parties' respective responsibilities. The letter of agreement clearly stated in bold italic type that supply on a named patient basis would stop as soon as the marketing authorization had been obtained. The medicine would then be charged at the basic NHS cost. The letter stated 'Due to the financial implications this will have for your hospital, a copy of this letter will be forwarded to your Chief Pharmacist'. A covering letter to the chief pharmacist confirmed details about the supply and its budgetary implications. Further, the Panel noted that the director of pharmacy at the trust in question wrote to Abbott about the budgetary implications of supply of Humira on a named patient basis before commencement of supply for any patient within the trust.

Shortly before the grant of the marketing authorization both the requesting rheumatologists and chief pharmacist were reminded by letter that free supply would cease.

The Panel considered that the overall arrangements for the supply of Humira on a compassionate basis within the trust were not unreasonable. It had been made sufficiently clear that the trust was expected to pay for Humira once the marketing authorization had been granted. The arrangements did not constitute the promotion of an unlicensed product prior to the grant of its marketing authorization and no breach of the Code was ruled.

The chief executive of an NHS Trust and a consultant physician complained about the free supply of Humira (adalimumab) on compassionate grounds by Abbott Laboratories Limited prior to the product being granted a marketing authorization in 2003.

COMPLAINT

The complainants were concerned about the financial impact of a medicine which, when unlicensed, had been provided free of charge on a compassionate basis but which, on receiving its marketing authorization, now had to be bought. The complainants considered that such a situation was open to exploitation.

The complainants explained that the trust in which they worked had inherited a significant financial liability following the licensing of Humira after it had previously been provided free of charge to one of its rheumatologists. As a result the trust had implemented a number of policies to prevent a recurrence, however the complainants considered that the way in which pharmaceutical companies made medicines available pre-launch, required investigation.

The complainants noted that in this particular case, the trust had been informed that Humira was made available, prior to licensing, to patients within the trust on compassionate grounds. The rationale for this compassionate provision was said to be the scarcity of the subcutaneous competitor, Enbrel (etanercept) and/or the inconvenience of travelling to the rheumatology centre for intravenous Remicade (infliximab). Both Enbrel and Remicade were licensed products.

The complainants stated that there were serious reasons to question this rationale. Firstly, both Enbrel and Remicade were funded for use and recommended by the National Institute for Clinical Excellence (NICE) whereas Humira was not funded, recommended or licensed. Secondly, the majority of patients offered Humira came from one geographical area served by one rheumatologist. Thirdly, patients under the care of the trust received Enbrel during this period. Finally, numerous patients from around the region were able to travel in to the rheumatology centre for Remicade treatment.

Whilst this raised governance issues within the trust it also raised questions around the role and responsibilities of Abbott.

The complainants stated that in correspondence with the company, Abbott had it made it clear that it 'received numerous requests to supply Humira to selected patients on a compassionate basis'. The complainants noted that at least 18 patients were treated locally before licensing and it was likely from Abbott's statement that many more around the UK were similarly treated. A conservative estimate of the additional (unexpected) cost to the trust for its patients was £120,000 per annum.

The complainants stated that as soon as Humira was licensed, Abbott immediately threatened the free supplies to those patients treated on compassionate grounds.

The complainants stated that the trust's view was that the provision of unlicensed medicines free of charge on compassionate grounds could be of great benefit to individual patients. The rationale for provision should however be more closely scrutinised to ensure that there was a clearly defined and agreed reason for such provision both by clinicians and pharmaceutical companies. Widespread provision on compassionate grounds of very expensive medicines prior to licensing undermined local fiscal planning and raised concerns around the motives of the suppliers, particularly as significant market-share could be achieved before the medicine was formally launched.

When writing to Abbott the Authority asked it to respond in relation to Clause 3.1 of the Code.

RESPONSE

Abbott explained that Humira received a marketing authorization in the European Union (EU) on 8 September 2003. It was a recombinant human monoclonal antibody directed against Tumour Necrosis Factor (TNF). Humira was a subcutaneous preparation licensed for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying anti-rheumatic drugs including methotrexate had been inadequate. Two other anti-TNF agents were licensed for use in RA; Remicade and Enbrel.

Remicade (licensed in the EU for RA in June 2000) was a chimeric monoclonal antibody administered as an intravenous infusion over a 2-hour period followed by repeat infusions at 2 and 6 weeks, and 8-weekly thereafter. Remicade contained non-human (murine) protein sequences, and both acute infusion reactions and delayed hypersensitivity reactions had been observed, in addition to development of neutralising anti-chimeric antibodies. Remicade must therefore be administered in the hospital setting, with appropriate resuscitative precautions, and in RA must be given concomitantly with methotrexate, an immunosuppressant.

Enbrel (licensed in the EU for RA in February 2000) was a human TNF receptor p75 Fc fusion protein presented as a subcutaneous preparation. During 2002 and 2003, there had been global supply shortages of Enbrel.

From mid 2002, and thus prior to the receipt of a marketing authorization for Humira, Abbott received numerous requests from clinicians to supply Humira to specific RA patients on a compassionate basis. This resulted from either intolerance to, lack of efficacy, or inappropriateness of licensed alternative agents based on clinical judgement, or their non-availability. As such these patients had no licensed available option.

It was for the prescriber to make clinical judgements for specific patients, not Abbott. In cases where compassionate supplies were requested, Abbott sought and received approval from the Medicines and Healthcare products Regulatory Agency (MHRA) to import and supply Humira in accordance with the relevant statutory instrument, and MHRA guidelines (MHRA Guidance Note No.14; 'The Supply of Unlicensed Relevant Medicinal Products for Individual Patients). In addition Abbott set its own conditions of supply to ensure that the prescriber knew his/her obligations when prescribing an unlicensed medicine, to ensure a comprehensive audit trail, to safeguard patient health, and to ensure that future financial implications were brought to the attention of key stakeholders in accordance with

Clause 3.1 of the Code. Every physician that formally requested compassionate supplies of Humira received a copy of these conditions and no product was supplied without these terms and conditions being accepted by the supervising physician. A copy was provided.

In all cases the letter of agreement between Abbott and the requesting physician was copied and sent to the chief pharmacist within the relevant hospital, and a covering letter attached drawing specific attention to potential budgetary implications. A copy of the letter was provided.

Abbott decided not to charge the NHS for product supplied pre-licence, and, upon receipt of a marketing authorization, to apply a commercial charge for all patients receiving Humira. This decision was made in consultation with the company's advisory board of consultant rheumatologists and directors of pharmaceutical services within the NHS.

Every attempt was made to bring this issue to the attention of key budget holders within the NHS, so that local processes to secure funding could be implemented well in advance of Humira gaining a marketing authorization. Abbott submitted that such activity was in accordance with Clause 3.1 of the Code, and represented an ethical and professional approach by Abbott to alert NHS budget holders to the potential for financial impact in their area.

Abbott stated that it had: clearly indicated its intention to charge for product post-licence in its letter of agreement with the requesting physician, and copied this letter to the chief pharmacist; drawn attention to the implications for local funding in the same letter; encouraged the physician to discuss potential budgetary implications with the chief pharmacist prior to requesting named patient supplies; in accordance with Clause 3.1 of the Code, notified all physicians and chief pharmacists/directors of pharmaceutical services involved in the provision of compassionate supplies of Humira, along with key NHS decision makers, of the positive scientific opinion for Humira, and associated cost implications for the NHS; in accordance with Clause 3.1 of the Code, written to remind key budget decision makers in the NHS, including all chief pharmacists/directors of pharmaceutical services, of the forthcoming availability of Humira and in accordance with Clause 3.1 of the Code, notified all physicians and chief pharmacists/directors of pharmaceutical services involved in the provision of compassionate supplies of Humira, along with key NHS decision makers, of the receipt of the marketing authorization for Humira, and associated cost implications for the NHS.

Abbott noted that copies of the relevant documentation referred to above were sent to the director of pharmacy services and the chief pharmacist at one of the hospitals within the complainants' trust and that copies of letters of agreement for doctors from the trust who prescribed Humira on a compassionate basis were also copied to the director of pharmacy services.

Abbott noted that the complainants had incorrectly implied that the provision of Humira was targeted geographically. The issues surrounding available licensed alternatives at that time affected the country as a whole, and Abbott received physician requests for pre-licence supply of Humira from throughout the UK.

Abbott noted that the complainants had referred to 'unexpected' costs to their trust arising on receipt of the marketing authorization for Humira and that Abbott threatened the free supplies to those patients treated on compassionate grounds on receipt of the marketing authorization for Humira. However, as described above, Abbott considered that it had taken every available opportunity to clearly communicate its intention to charge for Humira, at the basic NHS cost, once the marketing authorization was obtained.

In summary, Abbott considered that, faced with a demand for pre-licence supplies of Humira in 2002/2003, it supplied supervising physicians with compassionate use product in an ethical, responsible and professional manner, and in compliance with legislation and MHRA guidance. In recognition of the potential budgetary impact to the NHS, Abbott took all available steps to ensure that appropriate personnel were forewarned in advance of the grant of marketing authorization, such that local financial planning could be implemented.

In response to a request for further information Abbott noted that, although the complainants' letter referred to only one rheumatologist within their trust who received compassionate supplies of adalimumab, its records showed that two rheumatologists from this trust received such supplies. Abbott also confirmed that the requests that it had received for the provision of Humira on a compassionate basis were unsolicited.

Typically, there were several ways by which prescribers could become aware of the availability of a product pre-licence. These would also apply to Humira.

a) The number of specialist rheumatologists in the UK was relatively small and much information was exchanged by word of mouth. Academic updates in the therapeutic area were based around the annual high quality scientific meetings for health professionals involved in rheumatology of three major national/international organizations.

b) As doctors became aware, via the scientific community, of products reaching late stage development and entering the regulatory approval process, it was common for companies to receive direct enquiries regarding product information and/or compassionate supplies prior to receipt of a marketing authorization.

c) In addition, a number of clinicians who requested the supply of Humira on a compassionate basis had been involved in clinical trials of the product and would therefore have been aware of its advanced stage of clinical development.

d) Humira received a marketing authorization in the USA in December 2002. This resulted in an increased interest in Humira and requests for information and compassionate supplies.

e) From July to December 2002 Abbott UK held a number of scientific update meetings for consultant

rheumatologists, specialist registrars, specialist nurses, pharmacists, directors of pharmacy and health economists. These were in response to demand from these groups to be updated on scientific information on Humira, and health economic information regarding biologic therapies in RA. These meetings were strictly scientific and non-promotional. Records showed that neither of the rheumatologists based within the complainants' trust who received compassionate supplies of Humira attended these meetings.

Abbott stated that records showed that the first clinician at the trust in question initially requested general information regarding Humira in October 2002. The information sent was provided. This request was followed in November 2002 by a request from the same clinician for the supply of Humira on compassionate grounds for two patients. Prior to the supply of Humira to the trust for these or any further patients Abbott provided copies of the relevant documentation to the clinician, with copies sent to the chief pharmacist. No supplies of Humira were made available prior to the return of a signed copy of the terms and conditions of supply, which was received by Abbott dated 7 February 2003. Over the following 7 months this clinician requested compassionate supplies of Humira, anonymised details of which were provided.

The second clinician requested compassionate supplies of Humira for two patients in February 2003. Once again, prior to the supply of Humira to the trust for these patients Abbott provided the relevant documentation to the clinician, with copies sent to the chief pharmacist. No supplies of Humira were made available for these patients prior to the return of a signed copy of the terms and conditions of supply, which was received by Abbott dated 13 March 2003. The anonymised details of the patients for whom this clinician requested compassionate supplies of Humira were provided. This clinician did not request compassionate supplies of Humira for any further patients.

In January 2003 Abbott also received a letter from the director of pharmacy at the trust in question requesting details of the supply of Humira on a compassionate basis and specifically focussing on the potential financial implications for the trust on receipt of a marketing authorization. A member of Abbott's medical department telephoned the director of pharmacy to address the issues raised in the letter and in particular to discuss the proposed commercial charge for Humira. In addition, a copy of all relevant correspondence sent to the rheumatologists at issue relating to compassionate supplies of Humira had been copied to the pharmacy department at the hospital.

In the letter the director of pharmacy indicated that he knew one of the trust's clinicians was interested in receiving compassionate supplies of Humira. This letter was sent to Abbott in advance of commencement of supply of Humira for any patients at that trust and demonstrated that the pharmacy department of the trust was fully aware of the availability of Humira on compassionate grounds and the interest shown by one of the trust's clinicians in commencing patients on compassionate supplies. Abbott believed that this correspondence was out of line with the complainant's assertions that the cost of Humira on receipt of marketing authorization was 'unexpected'. Abbott also believed that sufficient awareness of the financial implications of commencing patients on compassionate supplies of Humira were demonstrated at the trust to have allowed appropriate fiscal planning.

All clinicians requesting compassionate supplies of Humira within the UK were required to provide Abbott UK with anonymised details supporting each patient request.

In most cases Humira was supplied because of intolerance to or non-availability of, licensed alternatives. However, in a minority of cases Humira was supplied due to lack of efficacy of licensed alternatives leading to deterioration in the clinical condition of the patient as judged by the supervising physician.

In the case of one of the rheumatologists, 2 of the 27 patients for whom requests for compassionate supplies were received had had previous trials of biologic therapies, namely Remicade and anakinra. Anakinra was a human interleukin-1 receptor antagonist licensed for the treatment of the signs and symptoms of RA in combination with methotrexate, in patients with an inadequate response to methotrexate alone. All other requests were based on intolerance to or lack of availability of licensed alternatives.

PANEL RULING

The Panel noted that it was not unacceptable for companies to provide medicines on a compassionate basis to patients who had participated in clinical trials and/or those who might benefit from treatment before the medicine was licensed and became commercially available. The Panel noted that such medicines must not be promoted prior to the grant of the marketing authorization as required by Clause 3.1 of the Code.

The Panel considered that the arrangements for the supply of unlicensed medicines on a named patient basis were potentially subject to the Code.

The Panel noted that the complainants had made a general complaint about the provision of unlicensed medicines for compassionate use. The Panel could only consider the supply by Abbott and not make a general ruling as arrangements would vary.

The Panel noted that whilst the complaint referred to the supply of Humira on a named patient basis to one unidentified rheumatologist Abbott stated that it had supplied the product to two rheumatologists within the trust.

The Panel examined the arrangements for the supply of Humira. Abbott submitted that requests resulted from intolerance, lack of efficacy or inappropriateness of licensed alternative treatments based on clinical judgement or non-availability. The signed request for compassionate supplies of Humira from the first rheumatologist had only stated that two of his

patients needed the product although no reason was given. The second rheumatologist had stated that two of his patients were unsuitable for currently available and licensed medicines. None of the anonymised patient record forms recorded why the patient had a special need for Humira. The Panel noted that the MCA (Medicines Control Agency; now known as the Medicines and Healthcare products Regulatory Agency) Guidance Note No.14 – The supply of unlicensed relevant medicinal products for individual patients – stated that responsibility for deciding whether an individual patient had 'special needs' which the licensed product could not meet should be a matter for the doctor responsible for the patient's care. This responsibility was reflected in the letter of agreement between Abbott and the requesting physician. The Panel noted the complainants' submission that patients under the care of the trust received Enbrel or travelled to a rheumatology centre for Remicade treatment during the relevant period. The Panel noted that the majority of the requests for compassionate supplies of Humira within the trust came from one physician who requested supplies for 27 patients.

The letter of agreement between Abbott and the requesting physician set out the conditions of named patient supply including the parties' respective responsibilities. Initially the company would supply only four Humira injections per request. It was the responsibility of the named physician or pharmacist to contact the company for continuation of supply.

The letter of agreement clearly stated in bold italic type that supply on a named patient basis would stop as soon as the marketing authorization had been obtained. The medicine would then be charged at the basic NHS cost. The letter stated 'Due to the financial implications this will have for your hospital, a copy of this letter will be forwarded to your Chief Pharmacist'. A covering letter to the chief pharmacist confirmed details about the supply and its budgetary implications. Further, the Panel noted that the director of pharmacy at the trust in question wrote to Abbott about the budgetary implications of supply of Humira on a named patient basis before commencement of supply for any patient within the trust.

Shortly before the grant of the marketing authorization both the requesting rheumatologists and chief pharmacist were reminded by letter that free supply would cease.

The Panel considered that the overall arrangements for the supply of Humira on a compassionate basis within the trust were not unreasonable. It had been made sufficiently clear that the trust was expected to pay for Humira once the marketing authorization had been granted. The arrangements did not constitute the promotion of an unlicensed product prior to the grant of its marketing authorization. No breach of Clause 3.1 was ruled.

Complaint received **18 March 2004**

Case completed **28 May 2004**

JANSSEN-CILAG/DIRECTOR v NAPP

Alleged breach of undertaking

Janssen-Cilag complained that a GP detail aid for Oxycontin issued by Napp and available on Napp's exhibition stand at a conference was the subject of a previous complaint (Case AUTH/1544/1/04) wherein the Code of Practice Panel had ruled breaches of the Code. The signed form of undertaking dated 13 February stated that the detail aid was last used on 24 December 2003. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Code of Practice Appeal Board.

Janssen-Cilag alleged a breach of the Code and that Napp had brought the industry into disrepute by its failure to withdraw the relevant materials once it had given an undertaking to do so, contrary to Clause 2.

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.

Janssen-Cilag had alleged that the GP detail aid at issue in the previous case, Case AUTH/1544/1/04, was present on Napp's promotional stand at a conference held at the end of February after the provision of the undertaking in acceptance of rulings made by the Panel.

The parties' accounts differed. Napp denied that the detail aid was available on the stand. Janssen-Cilag's medical adviser submitted that he had noticed the detail aid whilst talking to a Napp representative at the stand. He then left the stand to ask a colleague to act as a witness whilst he returned to obtain the detail aid and other items.

The Panel noted Napp's explanation of the arrangements for the delivery of promotional material to the conference by its logistics company. The GP detail aid did not appear on the order form.

When notified about this matter at the time by Janssen-Cilag, Napp had undertaken an item-by-item review of the material on the stand and had not found the detail aid at issue. The Panel noted Napp's account of its interviews with its representatives and that Napp was confident that the GP detail aid had not been brought to the conference by Napp personnel. The detail aid at issue was aimed at primary care, rather than the secondary care, palliative care specialists attending the conference.

Napp had stated that the detail aid was last used on in December 2003 at the end of its promotional cycle and prior to the provision of the undertaking in the previous case. Napp had arranged for the destruction of the material and explained that representatives were asked to return the material so that the logistics company could destroy the materials on 16 January 2004. The logistics company confirmed that as from that date it had no supplies of the GP detail aid to send out. Representatives were under a standing instruction to return superseded material at the end of a sales cycle. There was no documentation, however, to show that each representative had followed this instruction. At a sales conference in January representatives were twice reminded verbally to return remaining old materials. Further to the subsequent acceptance of the Panel's rulings in the previous case, on 13 February, Napp did not send its sales force a specific reminder.

The Panel was not satisfied that the arrangements for withdrawal of superseded material were sufficient. It had not been made sufficiently clear to the sales force that the material at issue was in breach of the Code and thus they were not aware that it was especially important not to reuse the material or make closely similar verbal claims.

Nonetheless the Panel had to determine whether the detail aid at issue was available from Napp's exhibition stand at the conference. The parties' accounts differed. A judgement had to be made on the available evidence. It was not possible to determine where the truth lay. The Panel was thus obliged to rule no breach of the Code.

Janssen-Cilag Ltd complained that a GP detail aid for Oxycontin (ref OX03019) issued by Napp Pharmaceuticals Limited and available on Napp's stand at the 2nd Bristol Opioid Conference, 26/27 February 2004, was the subject of a previous complaint (Case AUTH/1544/1/04) wherein the Code of Practice Panel had ruled breaches of the Code.

When the complaint now under consideration was received, Case AUTH/1544/1/04 was not completed as some rulings were subject to appeals from both parties. Nonetheless some rulings of breaches of the Code had already been accepted by Napp and in a signed form of undertaking and assurance dated 13 February 2004, it was stated that the GP detail aid was last used on 24 December 2003. As the complaint involved an alleged breach of undertaking it was taken up by the Director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Code of Practice Appeal Board.

COMPLAINT

Janssen-Cilag explained that its medical adviser was a delegate at the conference and whilst he was talking to the sales representatives from Napp, he recognised the detail aid at issue prominently displayed on the right hand side of the stand. The detail aid was entitled 'For moderate to severe cancer or post operative pain' and he recognised it due to its distinctive pink border at the top of the front cover. He stopped his discussion with the Napp sales representative temporarily and left to notify Janssen-Cilag's national medical liaison manager to act as a witness. He then returned and took copies of promotional material from the stand including a copy

of the detail aid in question. He could not recall if there were any other copies of the detail aid left on the stand once he had taken his copy.

Janssen-Cilag stated that Napp had given written assurances to the Authority on 13 February that the GP detail aid had been withdrawn. Napp had also previously stated in its response to the Code of Practice Panel to Case AUTH/1544/1/04 that the materials in question were no longer in circulation. This was clearly not the case, as a copy of the detail aid was obtained on 26 February from Napp's stand.

Janssen-Cilag alleged a breach of Clause 22 of the Code and that Napp had brought the industry into disrepute by its failure to withdraw the relevant materials once it had given an undertaking to do so, contrary to Clause 2.

RESPONSE

Napp submitted that it was not in breach of its undertaking dated 13 February. In its undertaking, Napp confirmed that the date on which the detail aid at issue and a leavepiece (UK/OX-03028a) were last used was 24 December, and it gave an assurance to take all possible steps to avoid similar breaches of the Code occurring in future. The withdrawn materials had been destroyed even before they were ruled to be in breach of the Code on 3 February and the date of its undertaking.

Napp stated that only four pharmaceutical companies were present at the meeting: Napp, Janssen-Cilag, Link Pharmaceuticals, and Cephalon. The Napp stand was on the left-hand side at the back of the room, while the Janssen-Cilag stand was on the right, with approximately 15 yards between them. There was a stage and lectern for presenters at the front of the room, and the middle was filled with seating for conference delegates. It was not possible for discussion to take place at the company stands during the lectures and so company stands were only manned before the first presentations started at approximately 10am and during breaks in the presentations. At other times Napp's representatives sat in the main seating area and listened to the presentations.

Given the space constraints, each company's stand was small – roughly the size of a desk. There were leavepieces, detail aids, slide dose converters and several other promotional items for Transtec on one half of the stand and OxyContin leavepieces, posters, patient diaries and other promotional items on the other half. Napp had ordered the sales materials for display at the meeting from a logistics company. A copy of the order form was provided. The product code for each item was displayed on the left column of the order form. Neither the detail aid at issue nor the leavepiece (UK/OX0-03028a) were among the materials ordered. The logistics company delivered the items directly to the conference location.

The sales material order form showed that Napp ordered two packs of 50 cancer pain leavepieces (UK/OX-03030 and two packs of 5 cancer sales aids (UK/OX-03051). Copies of each were provided. Although having only 10 sales aids on the stand might seem a small number, these were not intended to be distributed to delegates but rather to be used as a tool for discussion. Only two or three sales aids were displayed on the stand at any one time, with a reserve supply kept behind the stand. The cancer pain sales aid had a light blue 'flash' across the top with the wording 'For Moderate to Severe Cancer Pain'. The GP detail aid at issue, which was no longer in use, featured a pink flash across the top and therefore would have stood out from the other items. Given that there were only 10 cancer sales aids on the stand and only two or three were put out at one time, it seemed highly improbable that a copy of the GP detail aid would not have been spotted by one of Napp's representatives on the stand.

Napp submitted that it was also relevant that this was a conference for secondary care, palliative care specialists. Napp's new GP detail aid was not sent to the stand (as could be seen from the sales material order form), and the company's representatives, even if they had copies of the old one available (which they did not), would simply have had no reason to bring a GP detail aid on to the stand at a secondary care conference.

Napp was told of Janssen-Cilag's concerns about the OxyContin materials used at the Bristol conference on Friday, 27 February, which was the second day of the two-day conference. On Friday at 08:30, Janssen-Cilag's medical adviser telephoned Napp's director of pharmacovigilance and medical services and stated that on the previous day, he was allegedly given a copy of the GP detail aid which Napp had previously undertaken to withdraw. He claimed to have a 'third party witness' to this event, but in fact, as stated in the complaint, this witness was another Janssen-Cilag employee, not an independent third party.

Napp stated that it was rather odd that he waited until the day after the alleged incident before raising it with anyone from Napp. If he was genuinely concerned that inappropriate materials were being distributed to conference delegates, Napp would have expected him to have drawn it to the attention of representatives on the stand there and then so that immediate action could be taken.

Promptly after receiving the call, Napp telephoned its director of medical affairs who was attending the conference and he immediately instructed the representatives on the stand to remove all promotional materials. He and the divisional manager then reviewed item-by-item approximately 200 pieces of promotional material on the stand and did not find a single copy of the GP detail aid.

Furthermore, each of Napp's representatives confirmed in separate interviews that they did not bring any materials to the meeting themselves as a sufficient stock had already been delivered by the logistics company. One of the representatives did not possess any OxyContin materials because he was on a sales team that promoted Transtec. Another representative was leaving Napp immediately following the conference, and she no longer held any materials. A third representative had OxyContin materials in the boot of his car but gave his assurance that they stayed there as the logistics company had

provided sufficient stocks of materials, and in any event his own materials did not include the withdrawn piece. Napp's assistant product manager, analgesics, organised the materials for the Napp stand at the conference and had arranged for the logistics company to deliver sufficient materials, so she had no reason to bring additional supplies. The divisional manager only attended the conference on Friday, after the alleged incident. Neither the divisional manager not the director of medical affairs held stocks of promotional materials or brought any to the conference. Napp was confident, therefore, that the GP detail aid was not brought on to the stand by Napp personnel.

Napp's representatives' account of the exchange with Janssen-Cilag's medical adviser differed in several key respects from the version set out in complaint. Two of Napp's representatives were on the stand together when he began collecting some of Napp's literature, at which point one of the representatives asked if he could help and asked him which hospital he worked. When he replied that he was with Janssen-Cilag, he was asked not to take so many pieces of each item, as they were meant for conference delegates. Janssen-Cilag's medical adviser did not initiate or engage in any conversation about Napp's products or materials. He replaced some of the materials and left the stand. He did not have any other member of Janssen-Cilag with him during this encounter. He did not point out that he had discovered the GP detail aid on the stand. Nor did any of Napp's representatives recall him returning to the stand on his own or with anyone else; after having initial contact, they would have recognised him if he had returned. Given the small size of the stand, it was highly unlikely that he could have approached the stand without being seen.

Napp representatives' account was at odds with the version set out in the complaint. Janssen-Cilag's medical adviser claimed that he was talking with a Napp representative and interrupted his conversation when he noticed the withdrawn GP detail aid. He claimed he then notified a witness before returning to collect the copy the detail aid and some other promotional items. According to Napp's version of events, he did not temporarily leave the stand before collecting promotional items, nor did he return later.

Janssen-Cilag's letter also stated that he could not recall if there were other copies of the GP detail aid left on the small desk-sized stand. If the item leapt out at him to the extent that he allegedly interrupted a conversation and left to find a witness, it was odd that he now could not remember if that was the sole copy or one of several, particularly as there were so few detail aids on the stand.

Napp noted that its representatives were aware of at least one Janssen-Cilag representative spending time at Napp's stand. During the opening address all Napp's representatives were seated watching the presentation, and the Napp stand was unmanned at the back of the room. One of Napp's representatives turned to check the stand and noticed that a Janssen-Cilag representative was sitting on the Napp stand. He appeared to be looking at the Napp literature, and he remained on the stand for the duration of the opening address. On returning from the lunch break when the Napp stand was briefly unattended, another Napp representative observed two Janssen-Cilag representatives standing by the Napp stand. As he approached, the two representatives returned to the Janssen-Cilag stand.

Napp was simply unable to explain how Janssen-Cilag's medical adviser could have picked up a copy of the GP detail aid from the company stand. Napp was confident that it did not put it there.

Napp submitted that as indicated in its undertaking dated 13 February, the item in question was last used on 24 December, which was Napp's final business day of 2003. Napp was closed until Monday, 5 January. On Wednesday, 7 January, its analgesic team ordered the destruction of various OxyContin materials that were at the end of their cycle, including the GP detail aid. This was set out in the bottom section of the e-mail dated 7 January from Napp to the logistics company. In the top half of the same e-mail the new materials for the sales force were ordered which were to be delivered in time for a sales conference in mid-January.

The aforementioned e-mail was followed by a 'Material Destruction Request' from Napp to the logistics company on 8 January, which requested destruction of various OxyContin materials, including the GP detail aid, on 16 January. This allowed time for materials to be returned to the logistics company from head office and the sales force for destruction on that date. Napp noted that at that point, the previous materials had not yet been ruled in breach of the Code and Napp had not yet given its undertaking. The materials were removed from circulation at the beginning of January in the ordinary course of the new sales cycle and not on an urgent basis.

The logistics company confirmed the destruction of the materials on 16 January. Its letter stated that these materials were removed from its system and that no further quantities could be despatched to Napp personnel from 16 January.

As the previous OxyContin materials were dealt with in the ordinary course of Napp's new sales cycle and were destroyed by the logistics company on 16 January, the company did not send its sales force a specific reminder to return the materials following the ruling of breach on 3 February because the materials were already out of circulation and destroyed. The sales force was under a standing instruction to return superseded material after the end of a sales cycle. In addition, they were trained on the new sales materials issued at a sales conference during the week of 19 January, when they were twice verbally reminded to return any remaining old materials, which should already have been returned.

Napp confirmed that the representatives responsible for Napp's stand at the Bristol Opioid Conference had passed the ABPI Medical Representatives Examination. These employees were all very experienced, responsible and trusted members of the company.

Napp submitted that it had complied with Clause 22 of the Code because its undertaking was effectively already complied with by the time it was issued on 13

February 2004. The materials had been withdrawn from circulation in the ordinary course of the end of a sales cycle and had been destroyed by the logistics company in mid-January. The sales force had been trained on the new materials, including a new GP detail aid, at a sales conference during the week of 19 January and twice verbally reminded to return any remaining end-of-cycle materials, as per standing instructions to them. The logistics company had confirmed that no copies of the withdrawn materials could have been sent to Napp personnel as from 16 January 2004. Only the items listed in the sales material order form were displayed on the Napp stand at the conference, and this was double-checked following the telephone call to Napp. None of its representatives recollected the encounter as described by Janssen-Cilag.

Napp believed that high standards have been maintained at all times in accordance with Clause 9.1 of the Code and did not see any basis for a Clause 2 breach for bringing the industry into disrepute. Napp had withdrawn and destroyed the old materials – even before they had been ruled in breach – early in 2004. New materials were issued at conference in mid-January. Upon learning of Janssen-Cilag's latest claim a day after it allegedly occurred, Napp immediately undertook a thorough review of all the material on the stand and did not find a single copy of the withdrawn detail aid. Napp believed these actions satisfied the high standards required by Clause 9.1 and did not bring the industry into disrepute.

In short, it remained a mystery to Napp how Janssen-Cilag's medical adviser could have acquired what appeared to be a single 'rogue' copy of the withdrawn GP detail aid at the conference.

FURTHER COMMENTS FROM JANSSEN-CILAG

In response to a request for comment on part of Napp's response Janssen-Cilag explained that the conference was a two-day scientific meeting, discussing existing and new treatment modalities in the field of cancer and non-cancer related pain. Janssen-Cilag agreed with Napp's description of the setting of the conference. Janssen-Cilag's version of what transpired differed from Napp's account in the following manner.

Janssen-Cilag's medical adviser noticed the GP detail aid whilst discussing something with the male Napp representative. He realised the significance of the detail aid being present on the Napp stand, and that this was a situation that he had not previously faced in his relatively short career within the pharmaceutical industry. He did not say anything to the Napp representatives, as he thought that they would withdraw the item and deny that the event had occurred if he had highlighted the issue at hand to them. He notified his colleague who he believed could act as an independent witness. He returned to the Napp stand and obtained several items, including the GP detail aid. He was under the impression that his colleague together with his word would suffice to uphold a complaint. He returned to the stand several times further on Thursday and on Friday morning and disputed the events as narrated by Napp. He did initiate a conversation with one of the representatives before obtaining the relevant materials. Unlike Napp's version of events, Janssen-Cilag did not replace some of the materials obtained (perhaps implying that he could have planted the item), rather he was told not to pick up a certain item by one of the representatives, as she stated that there were only a few copies of it. He even recollected asking a third member of the Napp staff later (either Thursday afternoon or Friday morning, he could not recall the exact time) if he could hand him another piece of promotional material, the piece that he was prevented from picking up by one of the representatives.

After he had obtained the GP detail aid, he was uncertain of how to proceed and initially telephoned his line manager, and subsequently later in the day he spoke to the medical director. He could not recall exactly when he telephoned Napp, but recalled that he rang on Friday morning. In this telephone call he stated to Napp that he had a witness to obtaining the detail aid, and could not recall saying that this witness was a non-pharmaceutical third party person. Napp was informed of what had happened within 24 hours of the event occurring, and the reasons for the delay in notification were that he went through his line manager and company medical director before proceeding to contact Napp.

He did not want to comment on the implicit allegation in Napp's letter that the actions of Janssen-Cilag's sales representatives could have resulted in the GP detail aid appearing on Napp's stand, apart from stating that he had nothing but the utmost respect in regard to the professional conduct of Janssen-Cilag's representatives.

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 Case AUTH/1544/1/04 concerned a complaint about, *inter alia*, the GP Oxycontin detail aid (ref OX03019) produced by Napp wherein Napp had provided an undertaking in relation to some of the rulings of breaches of the Code made by the Code of Practice Panel. The undertaking, dated 13 February, stated that the detail aid was last used on 24 December ie before the complaint about it had been received.

Turning to the present case, Case AUTH/1566/3/04, the Panel noted that Janssen-Cilag alleged that the GP detail aid at issue in the previous case, Case AUTH/1544/1/04 was present on Napp's promotional stand at a conference on 26 and 27 February, ie after the provision of the undertaking in acceptance of rulings made by the Code of Practice Panel and after Napp had stated that it was last used.

The Panel noted that the parties' accounts differed. Napp denied that the detail aid was available on the stand. Janssen-Cilag's medical adviser submitted that

he had noticed the detail aid whilst talking to a Napp representative at the stand. He then left the stand to ask a colleague to act as a witness whilst he returned to obtain the detail aid and other items. He denied that he replaced any materials on the stand as submitted by Napp.

The Panel noted Napp's explanation of the arrangements for the delivery of promotional material to the conference by its logistics company. The GP detail aid did not appear on the order form.

The Panel also noted that when notified about this matter by Janssen-Cilag, Napp had undertaken an item-by-item review of the material on the stand and had not found the detail aid at issue. The Panel noted Napp's account of its interviews with its representatives and that Napp was confident that the GP detail aid had not been brought to the conference by Napp personnel. The detail aid at issue was aimed at primary care, rather than the secondary care, palliative care specialists attending the conference.

The Panel noted Napp's submission that the detail aid was last used on 24 December at the end of its promotional cycle and prior to the provision of the undertaking in the previous case. Napp had arranged for the destruction of the material and explained that representatives were asked to return the material so that the logistics company could destroy the materials on 16 January. The logistics company confirmed that as from that date it had no supplies of the GP detail aid to send out. The Panel noted that the representatives were under a standing instruction to return superseded material at the end of a sales cycle. There was no documentation, however, to show that each representative had followed this instruction. At a sales conference in the week commencing 19 January representatives were twice reminded verbally to return remaining old materials. Further to the subsequent acceptance of the Panel's rulings in the previous case on 13 February, Napp did not send its sales force a specific reminder.

The Panel considered that an undertaking was an important document. The Panel was not satisfied that the arrangements for withdrawal of superseded material were sufficient to ensure that if the material were subsequently ruled in breach of the Code it was not reused. It had not been made sufficiently clear to the sales force that the material at issue was in breach of the Code and thus they were not aware that it was especially important not to reuse the material or make closely similar verbal claims.

Nonetheless the Panel had to determine whether the detail aid at issue was available from Napp's exhibition stand at the conference.

The parties' accounts differed. A judgement had to be made on the available evidence. It was not possible to determine where the truth lay. The Panel was thus obliged to rule no breach of Clauses 22 and 2 of the Code.

Complaint received **19 March 2004**

Case completed **1 June 2004**

LILLY v ASTRAZENECA

Seroquel leavepieces

Lilly complained about the promotion of Seroquel (quetiapine) by AstraZeneca. Two leavepieces were at issue. Lilly supplied Zyprexa (olanzapine).

In relation to a leavepiece, Lilly alleged that the claim 'STRONG *on* schizophrenia' was both misleading and a hanging comparison. The company assumed that the claim was intended to mean that Seroquel was at least as efficacious as other treatments for schizophrenia. Seroquel had demonstrated superior efficacy to placebo in improving psychotic symptoms but was not significantly different to haloperidol. A number of other atypical antipsychotics, including clozapine, amisulpride, risperidone and olanzapine had demonstrated superiority to haloperidol (Davies *et al*, 2003). Seroquel did not have adequate efficacy data to justify a claim of 'strong'.

The Panel noted the layout of the leavepiece in question. Immediately beneath the product logo was the claim 'STRONG *on* schizophrenia'. This was followed by a claim regarding unbeaten first-line efficacy, a statement about a new tablet strength and a claim for placebo level extrapyramidal symptoms across the full dose range. The Panel considered that the claim in question was a statement to the effect that Seroquel worked well in schizophrenia and the claims below were the reasons why. The Panel did not consider that the claim 'STRONG *on* schizophrenia' was a hanging comparison; Seroquel had not been described as stronger without stating that with which it was compared. No breach of the Code was ruled.

The Panel noted that Lilly had stated that there was not adequate efficacy data to justify the claim of 'strong'. Davis *et al*, a meta-analysis showed that Seroquel had demonstrated similar efficacy to first generation antipsychotics whereas other atypicals were shown to be superior. The statistical significance between Seroquel and the other typicals was not reported. The Panel noted that five Seroquel studies had been included compared with 22 for risperidone, 14 for olanzapine and 12 for amisulpride. The meta-analysis of Tandon and Jibson (2003) submitted by AstraZeneca concluded that data thus far did not support assertions of differential efficacy between risperidone, olanzapine and quetiapine. NICE reported that the evidence it had considered suggested that the atypicals were at least as effective as the typical agents in terms of overall response rate and that although there might be variations in their relative effects on positive and negative symptoms and relapse rates there was inadequate data to separate them.

The Panel noted that although there were fewer trials with Seroquel there was no data to show that it was not efficacious in the treatment of schizophrenia or that it was statistically significantly less efficacious than other treatments. The Panel thus did not consider that the claim 'STRONG *on* schizophrenia' was misleading as alleged. No breach of the Code was ruled.

Lilly alleged that the claim "Seroquel' has unbeaten first-line efficacy' was misleading. Meta-analysis of randomised controlled trials studying the efficacy and extrapyramidal side-effects of olanzapine, Seroquel, risperidone and sertindole compared to conventional antipsychotics and placebo demonstrated that all the atypical antipsychotics had superior efficacy to placebo (Leucht *et al*, 1999). Sertindole and Seroquel were as effective as haloperidol and olanzapine and risperidone were more effective than haloperidol for symptomatic treatment of schizophrenia. In a prospective observational study of ten thousand schizophrenic outpatients in Europe the mean change in positive schizophrenia symptoms and overall clinical improvement after 6 months' treatment was less for Seroquel-treated patients than for patients treated with risperidone, olanzapine and clozapine (Haro *et al* 2003). Seroquel did not have unbeaten first-line efficacy.

The Panel noted that the claim "Seroquel' has unbeaten first-line efficacy' was referenced to Tandon and Jibson (2003) and Tandon *et al* (2001). The Panel noted its comments on Tandon and Jibson and the NICE guidance above. The Panel also noted the parties' submissions on the methodology and outcome data of Leucht *et al* and Haro *et al*.

The Panel considered that the claim "Seroquel' has unbeaten first-line efficacy' was a fair reflection of the balance of the data and was not misleading in this regard. No breach of the Code was ruled.

Lilly alleged that the claim "Seroquel' is the only first-line atypical with placebo level EPS' was misleading because Seroquel was not the only first-line atypical with this information in the summary of product characteristics (SPC). For instance, Section 4.8 of the Zyprexa SPC stated, 'In clinical trials, the incidence of parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo'.

In addition there were numerous case reports of patients treated with Seroquel developing EPS after starting treatment.

The Panel noted that Lilly had misquoted the claim at issue which read "Seroquel' is the only first-line atypical with placebo level EPS (including akathisia) across the full dose range'.

The Seroquel SPC stated that the results of three placebo-controlled clinical trials, including one that used a dose range of Seroquel of 75mg to 750mg/day, identified no difference between Seroquel and placebo in the incidence of EPS or use of concomitant anticholinergics. The Panel noted from the SPC that for the treatment of schizophrenia the usual effective dose of Seroquel was 300mg to 450mg/day. Depending on clinical response and tolerability the dose could be adjusted within the range of 150mg to 750mg/day.

The Panel noted that the Zyprexa SPC stated that in clinical trials the incidence of parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of parkinsonism, akathisia, and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it could not be concluded at present that olanzapine produced less tardive dyskinesia and/or tardive extrapyramidal syndromes. The risperidone SPC stated that the incidence and severity of extrapyramidal symptoms were significantly less than with haloperidol.

The Panel noted that Arvanitis *et al* (1997) concluded that Seroquel was no different to placebo across the dose range studied (75, 150, 300, 600 or 750mg daily) regarding the incidence of EPS. The Panel noted that the Seroquel SPC referred to the incidence of EPS throughout the dose range of 75 to 750mg/day. Information about the incidence of EPS in relation to the dose range did not appear in the Zyprexa or risperidone SPCs.

On the information before it the Panel considered that the claim "Seroquel' is the only first-line atypical with placebo level EPS (including akathisia) across the full dose range' was not misleading as alleged. No breach of the Code was ruled.

Lilly alleged that the phrase 'Towards Equilibrium Fast' was a claim that Seroquel had a fast onset of action which was misleading. No references were cited. However, a second leavepiece cited Jones and Huizar (2003) in support of this claim. The study described compared the efficacy of Seroquel and placebo for the treatment of mania. Seroquel was significantly more efficacious than placebo after 4 days of treatment. Seroquel must have the dose titrated up to a therapeutic level. The SPC stated that the usual effective dose was in the range 400-800mg/day. It required 4 days to titrate Seroquel up to 400mg, which provided an explanation for the delayed efficacy. Many other treatments for acute mania did not require dose titration. Olanzapine therapy achieved an efficacious dose on the first day of treatment. Given that Seroquel required dose titration and other therapies produced significant improvement in symptoms before Seroquel had even reached an effective dose the claim 'Towards Equilibrium Fast' was misleading.

The Panel noted that the claim 'Towards Equilibrium Fast' appeared on a page which discussed Seroquel's new indication in mania associated with bipolar disorder. The Panel did not accept Lilly's assertion that this was a claim for a fast onset of action. Equilibrium was defined as a well-balanced state of mind or feeling, equanimity (ref: The New Shorter Oxford English Dictionary 1993). Within the context of the disease, mania associated with bipolar disorder, the Panel considered that 'Towards Equilibrium Fast' referred to the reduction of manic symptoms. The Panel did not consider that the Seroquel dose titration regimen at days 1-4 in itself meant that Seroquel did not move a patient towards equilibrium fast. The Panel noted that Jones and Huizar showed that Seroquel significantly reduced the severity of mania as measured by the Young Mania Rating Scale (YMRS) at day 4, $p<0.05$ versus placebo. The statistically significant difference between the two, in favour of Seroquel, was maintained until the end of the trial at day 84.

The Panel noted the parties' submissions about the onset of action of olanzapine but did not consider that the claim was directly or implicitly comparative.

Given Jones and Huizar the Panel did not consider the claim 'Towards Equilibrium Fast' unreasonable or misleading as alleged. No breach of the Code was ruled.

In relation to the second leavepiece, Lilly stated that the claims 'Lasting improvement in mania symptoms' and 'Fast and lasting improvement in mania symptoms over three months' referred to the long-term benefits of Seroquel monotherapy. Lilly stated that Seroquel was indicated for manic episodes associated with bipolar disorder and was not licensed for relapse prevention in bipolar disorder. This claim was therefore a breach of the Code.

The Panel noted that Seroquel was indicated, *inter alia*, for the treatment of manic episodes associated with bipolar disorder. The Panel noted Lilly's allegation that 'Lasting improvement in mania symptoms' and 'Fast and lasting improvement in mania symptoms over three months' were claims for long-term benefits and Seroquel was not licensed for relapse prevention in bipolar disorder.

There was no reference to duration of treatment in the Seroquel SPC. The claim 'Fast and lasting improvement in mania symptoms over three months' was referenced to Jones and Huizar in which the primary objective was to assess the change from baseline in Young Mania Rating Scale (YMRS) score at day 21. Secondary endpoints assessed at day 21 and day 84 included the YMRS response rate ($\geq$ 50% reduction in YMRS score) and YMRS remission rate (YMRS score $\leq$ 12). The data showed that the reduction from baseline for the YMRS score for Seroquel was statistically significantly greater than placebo from day four onwards ($p=0.021$), $p<0.001$ at day 84 (versus placebo). Response and remission rates were also significantly greater with Seroquel than placebo at days 21 and 84 for the YMRS.

The Panel noted that Seroquel was not licensed for prevention of relapse. There was no reference to duration of treatment in the Seroquel SPC. The Panel considered that the claims at issue referred to maintenance of response as measured by the YMRS score. Maintenance of response was not the same as prevention of relapse. The Panel did not consider that either claim implied that Seroquel was indicated for prevention of relapse as alleged. No breach of the Code was ruled.

Eli Lilly & Company Limited complained about the promotion of Seroquel (quetiapine) by AstraZeneca UK Limited. Two four page leavepieces were at issue. Lilly supplied Zyprexa (olanzapine).

A Leavepiece ref A45242

1 Claim: STRONG *on* schizophrenia

This claim appeared at the top of one page of the four page leavepiece beneath the brand name and logo. 'STRONG' appeared on one line followed by '*on* schizophrenia' on the consecutive line.

COMPLAINT

Lilly alleged that the claim was both misleading and a hanging comparison in breach of Clause 7.2. The company assumed that the claim was intended to mean that Seroquel was at least as efficacious as other treatments for schizophrenia. Seroquel had demonstrated superior efficacy to placebo in improving psychotic symptoms but was not significantly different to haloperidol. A number of other atypical antipsychotics, including clozapine, amisulpride, risperidone and olanzapine had demonstrated superiority to haloperidol (Davies *et al*, 2003). Seroquel did not have adequate efficacy data to justify a claim of 'strong'.

RESPONSE

AstraZeneca explained that 'Strength' described the efficacy of Seroquel in treating the signs and symptoms of schizophrenia. It was not a comparative claim or a hanging comparison as might be expressed in the phrase, 'Stronger on schizophrenia'.

There was a large database of evidence in different patient settings that demonstrated Seroquel was effective in the treatment of schizophrenia, ie 'strong on schizophrenia'. Therefore the claim was not misleading.

In relation to evidence of the strength of Seroquel vs conventional antipsychotics AstraZeneca submitted that Lilly was wrong to state that Seroquel was not significantly different to haloperidol. Randomised clinical trials had shown Seroquel to be as effective as the conventional antipsychotics haloperidol and chlorpromazine in the treatment of schizophrenia but with a better tolerability profile. In a meta-analysis of trials vs haloperidol, Seroquel was shown to be superior in treating the symptoms of schizophrenia (AstraZeneca Data on file). In addition, haloperidol had for many years been considered the gold standard in antipsychotic therapy, therefore a result of 'as effective as' was a testament to the 'strength' of Seroquel.

In relation to evidence of strength vs atypical antipsychotics the efficacy of Seroquel against these agents had been established in a number of settings. Seroquel had been shown to be as effective as risperidone in the treatment of schizophrenia in two large, double-blind and naturalistic trials (Tandon *et al* 2001; Zhong *et al* 2003). Sacchetti *et al* (2003), an interim analysis of a single-blinded comparison of Seroquel, olanzapine and risperidone, suggested that the efficacy of these three first-line atypicals was similar, with a slight numerical superiority for Seroquel. Being an interim analysis though, no definitive conclusions could yet be drawn. The efficacy of Seroquel in treating patients that had been inadequately treated with olanzapine therapy had also been proven (Larmo 2003).

A recent meta-analysis of all published, short-term, randomised, controlled trials involving Seroquel, olanzapine and risperidone concluded '… the evidence from the currently available published clinical trials, analysed by two different approaches, clearly and consistently shows that the available first-line atypical agents are essentially equivalent to one another in efficacy terms' (Tandon and Jibson 2003).

In addition, the National Institute for Clinical Evidence (NICE) issued guidance in June 2002 based on its assessment of 172 randomised controlled trials of first-line atypicals in the treatment of schizophrenia. This compared to the 124 trials included in the Davies *et al* meta-analysis cited by Lilly. The NICE guidance concluded that 'the evidence considered suggests that the atypical antipsychotics are at least as efficacious as the typical agents in terms of overall response rates…there are inadequate data to enable separate evaluation of the overall impact of individual atypicals on schizophrenia'.

Referring to the Davis meta-analysis, AstraZeneca stated two further in-house meta-analyses of double-blind, controlled trials showed Seroquel to be superior to haloperidol for the treatment of schizophrenia using the common primary endpoints Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) response (≥ 40%).

The inclusion in the Davis meta-analysis of trials where more than one primary common endpoint was used ie BPRS, PANSS, Clinical Global Impression (CGI) reduced confidence in the robustness of this analysis. AstraZeneca alleged that the meta-analysis was flawed, which had resulted in a bias against Seroquel because:

1 it included trials where clinically non-optimal, low doses (150mg/day) of Seroquel were administered but excluded non-optimal, low doses of risperidone (2mg/day) or olanzapine (5mg/day). The summary of product of characteristics (SPC) for Seroquel (Section 4.2) stated that 'the dose should be titrated to the usual effective dose range of 300 to 450 mg/day'.

2 a comparative trial vs risperidone (QUEST) showing comparative efficacy (De Nayer *et al* 2003) was excluded.

AstraZeneca denied that the claim 'Strong on schizophrenia' was either a hanging comparison or misleading. The balance of up-to-date information supported the 'strength' of Seroquel in schizophrenia.

PANEL RULING

The Panel noted the layout of the leavepiece in question. Immediately beneath the product logo was the claim 'STRONG *on* schizophrenia'. This was followed by a claim regarding unbeaten first-line efficacy, a statement about a new tablet strength and a claim for placebo level extrapyramidal symptoms across the full dose range. The Panel considered that

the claim in question was a statement to the effect that Seroquel worked well in schizophrenia and the claims below were the reasons why. The Panel did not consider that the claim 'STRONG *on* schizophrenia' was a hanging comparison; Seroquel had not been described as stronger without stating that with which it was compared. No breach of Clause 7.2 was ruled.

The Panel noted that Lilly had stated that there was not adequate efficacy data to justify the claim of 'strong'. The Davis *et al* meta-analysis had shown that Seroquel had demonstrated similar efficacy to first generation antipsychotics whereas other atypicals were shown to be superior. The statistical significance between Seroquel and the other typicals was not reported. The Panel noted that five Seroquel studies had been included in the meta-analysis compared with 22 for risperidone, 14 for olanzapine and 12 for amisulpride. The meta-analysis of Tandon and Jibson concluded that data thus far did not support assertions of differential efficacy between risperidone (n=2090), olanzapine (n=1799) and quetiapine (n=541). NICE reported that the evidence it had considered suggested that the atypicals were at least as effective as the typical agents in terms of overall response rate and that although there might be variations in their relative effects on positive and negative symptoms and relapse rates there was inadequate data to separate them.

The Panel noted that although there were fewer trials with Seroquel there was no data to show that it was not efficacious in the treatment of schizophrenia or that it was statistically significantly less efficacious than other treatments. The Panel thus did not consider that the claim 'STRONG *on* schizophrenia' was misleading as alleged. No breach of Clause 7.2 was ruled.

2 Claim: "Seroquel' has unbeaten first-line efficacy'

This appeared beneath the claim at issue at point 1.

COMPLAINT

Lilly alleged that this claim was misleading, in breach of Clause 7.2. Another meta-analysis of randomised controlled trials studying the efficacy and extrapyramidal side-effects of olanzapine, Seroquel, risperidone and sertindole compared to conventional antipsychotics and placebo demonstrated that all the atypical antipsychotics had superior efficacy to placebo (Leucht *et al*, 1999). Sertindole and Seroquel were as effective as haloperidol and olanzapine and risperidone were more effective than haloperidol for symptomatic treatment of schizophrenia. In a prospective observational study of ten thousand schizophrenic outpatients in Europe the mean change in positive schizophrenia symptoms and overall clinical improvement after 6 months' treatment was less for Seroquel-treated patients than for patients treated with risperidone, olanzapine and clozapine (schizophrenia outpatient health outcomes (SOHO) study; Haro *et al* 2003). Seroquel did not have unbeaten first-line efficacy.

RESPONSE

AstraZeneca stated that Leucht *et al* had been superseded by two more recent meta-analyses ie the NICE review and that by Tandon and Jibson (2003). Both meta-analyses concluded that at present no single atypical antipsychotic currently licensed for first-line use had an advantage over the others. AstraZeneca recognised the superior data for clozapine but excluded this medicine from the current considerations as it was not licensed for first-line use in schizophrenia.

The outdated review by Leucht *et al* was neither fair nor complete and was biased against Seroquel because patients took sub-optimal doses of Seroquel (<300mg/day) in all of the six trials included in the analysis. The Seroquel SPC stated that the usual effective dose range in the treatment of schizophrenia was 300-450mg/day. Removal of those trials that included sub-optimal Seroquel dosing gave a positive outcome for the product, confirmed by an overlapping of confidence intervals with comparator first-line atypicals. A further meta-analysis showed Seroquel to be superior to haloperidol in improving both the positive and negative symptoms of schizophrenia (AstraZeneca data on file).

Tandon and Jibson reviewed all published, short-term, randomized, controlled trials involving Seroquel, olanzapine and risperidone that used the PANSS score to measure effectiveness. PANSS was utilized because it was the most commonly used tool to assess clinically relevant symptoms. This strict criteria for inclusion made this meta-analysis unique in that other meta-analyses, such as that by Davies *et al* tried to draw conclusions using non-standard endpoints, ie comparing a response rate where the BPRS was reduced by 30% in one trial, with a response rate defined as a BPRS reduction of 40% in another.

The improvement in PANSS seen with Seroquel, olanzapine and risperidone was 18.5, 18.2, and 18.8 (p=ns between groups) respectively ie these first-line atypicals were essentially equivalent.

AstraZeneca noted Lilly's reference to the SOHO study. SOHO was a 3-year, observational, unblinded, Lilly sponsored study. AstraZeneca refuted the use of claims based on SOHO for several reasons. Firstly claims based on a 6-month interim report of a 3-year trial had to be considered with caution. The choice of antipsychotic was based on patients' clinical need rather than by true randomization therefore it was difficult to consider the role of confounding factors when reviewing outcome. Though an observational study, no account had been made of other care that could influence patient outcomes, eg the effect of non-pharmacological patient care that was known to greatly influence outcomes in this patient group. Conclusions from observational studies should be interpreted with caution as bias was more likely than in double-blind randomized controlled trials. The main tool used to measure efficacy was the non-robust clinical global improvement scale (CGI), which was a subjective measure of symptom improvement, not an objective measure. The size of the Seroquel cohort was small (15%) compared to that of olanzapine.

Unfortunately the interim analysis made no reference to dose but another 6-month interim analysis of SOHO did allude to the doses of Seroquel used. This demonstrated that for over half of this analysis period the modal dose of Seroquel used was a clinically sub-optimal 200mg. Although the mean change in positive symptoms and overall symptoms favoured clozapine and olanzapine over other therapies, there was a significant overlap in the confidence intervals between Seroquel, amisulpride, and risperidone. This implied that it was too early to draw firm conclusions concerning efficacy. This trial design was not robust and biased against Seroquel, therefore results must be interpreted with caution.

AstraZeneca considered that the claim "Seroquel' has unbeaten first-line efficacy in the treatment of schizophrenia' was supported by balanced, fair, and objective evidence.

PANEL RULING

The Panel noted that the claim "Seroquel' has unbeaten first-line efficacy' was referenced to Tandon and Jibson (2003) and Tandon *et al* (2001). The Panel noted its comments on Tandon and Jibson and the NICE guidance at point A1 above. The Panel also noted the parties' submissions on the methodology and outcome data of Leucht *et al* and Haro *et al*.

The Panel considered that the claim "Seroquel' has unbeaten first-line efficacy' was a fair reflection of the balance of the data and was not misleading in this regard. No breach of Clause 7.2 was ruled.

3 Claim: "Seroquel' is the only first-line atypical with placebo level EPS (including akathisia) across the full dose range'

COMPLAINT

Lilly alleged that the claim "Seroquel' is the only first-line atypical with placebo level EPS', which was referenced to the Seroquel, risperidone and amisulpride SPCs and two clinical trials, was in breach of Clause 7.2. The Seroquel SPC mentioned seven clinical trials in which the incidence of extrapyramidal symptoms (EPS) did not differ between Seroquel and placebo-treated patients. The claim was misleading because Seroquel was not the only first-line atypical with this information in the SPC. For instance, Section 4.8 of the Zyprexa SPC stated, 'In clinical trials, the incidence of parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo'.

In addition there were numerous case reports of patients treated with Seroquel developing EPS after starting treatment (Kropp *et al*, 2004, Prueter *et al*, 2003, Sharma 2003).

RESPONSE

AstraZeneca noted that in the leavepiece at issue the claim read 'Seroquel is **the only** first-line atypical with placebo-level EPS (including akathisia) **across the full dose range**'. This claim, as used in totality, was not misleading. AstraZeneca did not use the claim in the form stated by Lilly on any current piece of promotional material.

The claim was consistent with the Seroquel SPC, Section 5.2 of which stated, 'The results of three placebo-controlled clinical trials, including one that used a dose range of Seroquel of 75 to 750mg/day, identified no difference between Seroquel and placebo in the incidence of EPS or use of concomitant anticholinergics'.

Other references substantiated this claim, in particular Arvanitis *et al* (1997) demonstrated that the incidence of EPS at various fixed doses was similar to placebo (150mg-6%, 300mg-4%, 600mg-8%, 750mg-6%, placebo-18%). No significant difference was shown between placebo and Seroquel for all administered doses. This supported the claim that Seroquel was the only first-line atypical with placebo-level EPS across the full-dose range.

The complaint centred on the assertion that Zyprexa was also a first-line atypical with placebo level EPS (including akathisia) across the full-dose range. Although Lilly had referred to Section 4 of the Zyprexa SPC, the full statement referred stated that 'Olanzapine-treated patients had a lower incidence of parkinsonism, akathisia, and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it can not be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes'.

Unlike the Seroquel SPC, the Zyprexa SPC did not state that a placebo-like incidence of EPS was seen across the full-dose range for olanzapine.

The incidence of EPS with olanzapine was significantly greater than placebo at higher licensed doses, as stated by the Physicians Desk Reference (PDR). Patients on the highest licensed dose of olanzapine (20 mg) suffered twice as much from EPS as did those taking placebo (32% vs 16%, $p<0.05$).

AstraZeneca highlighted an earlier inter-company complaint resolved on 10 December 2001. The claim 'No increased risk of EPS with increasing dose with the therapeutic range' appeared on a Zyprexa leavepiece (ZY803). Lilly agreed 'the current body of evidence does not safely sustain that claim' and agreed to remove the claim from all promotional material until evidence became available to support it. AstraZeneca believed that current evidence was still not available to support this claim thus it considered that the claim 'Seroquel is the only first-line atypical with placebo-level EPS across the full-dose range' was still valid and not misleading.

In addition, Lilly referred to case reports of EPS occurring in patients who were treated with Seroquel. Single-case reports were recognized as being of little value when compared to large double-blind randomized controlled trials. These case reports referred to patients who AstraZeneca would assert were predisposed to EPS including those who had previously experience EPS with other therapies and patients suffering from Parkinson's Disease. Case

reports also existed where EPS had occurred in patients treated with olanzapine.

AstraZeneca therefore stood by its claim that Seroquel was the only first-line atypical with placebo level EPS across the full-dose range as evidenced by up-to-date balanced information including that on the Seroquel SPC.

PANEL RULING

The Panel noted that Lilly had misquoted the claim at issue. It read "Seroquel' is **the only** first-line atypical with placebo level EPS (including akathisia) **across the full dose range**'.

Section 5.1 of the Seroquel SPC stated that the results of three placebo-controlled clinical trials, including one that used a dose range of Seroquel of 75mg to 750mg/day, identified no difference between Seroquel and placebo in the incidence of EPS or use of concomitant anticholinergics. The Panel noted from the SPC that for the treatment of schizophrenia the usual effective dose of Seroquel was 300mg to 450mg/day. Depending on clinical response and tolerability the dose could be adjusted within the range of 150mg to 750mg/day.

The Panel noted that Section 4.8 of the Zyprexa SPC stated that in clinical trials the incidence of parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of parkinsonism, akathisia, and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it could not be concluded at present that olanzapine produced less tardive dyskinesia and/or tardive extrapyramidal syndromes. Section 4.8 of the risperidone SPC stated that the incidence and severity of extrapyramidal symptoms were significantly less than with haloperidol.

The Panel noted that Arvanitis *et al* concluded that Seroquel was no different to placebo across the dose range studied (75, 150, 300, 600 or 750mg daily) regarding the incidence of EPS. The Panel noted that the Seroquel SPC referred to the incidence of EPS throughout the dose range of 75 to 750mg/day. Information about the incidence of EPS in relation to the dose range did not appear in the Zyprexa or risperidone SPCs. The Panel noted AstraZeneca's submission about the single case reports referred to by Lilly.

On the information before it the Panel considered that the claim "Seroquel' is the only first-line atypical with placebo level EPS (including akathisia) across the full dose range' was not misleading as alleged. No breach of Clause 7.2 was ruled.

4 Claim: 'Towards Equilibrium Fast'

This claimed appeared as a strapline beneath the product logo on the other outside cover of the leavepiece on a page headed 'New in mania associated with bipolar disorder'.

COMPLAINT

Lilly alleged that 'Towards Equilibrium Fast' was a claim that Seroquel had a fast onset of action which was misleading, in breach of Clause 7.2 of the Code. No references were cited. However, another leavepiece (Ref A45241) cited Jones and Huizar (2003) in support of this claim. The study described compared the efficacy of Seroquel and placebo for the treatment of mania. Seroquel was significantly more efficacious than placebo after 4 days of treatment. Seroquel must have the dose titrated up to a therapeutic level. The SPC stated that the usual effective dose was in the range 400-800mg/day. It required 4 days to titrate Seroquel up to 400mg, which provided an explanation for the delayed efficacy. Many other treatments for acute mania did not require dose titration. For instance, olanzapine therapy achieved an efficacious dose on the first day of treatment. Furthermore, a study comparing the efficacy of olanzapine and valproate for treatment of acute mania demonstrated that olanzapine produced a significantly greater improvement than valproate after 2 days of treatment (Tohen *et al* 2002). Given that Seroquel required dose titration and other therapies produced significant improvement in symptoms before Seroquel had even reached an effective dose the claim 'Towards Equilibrium Fast' was misleading.

RESPONSE

AstraZeneca denied that the claim was misleading. The claim did not, as alleged, refer solely to the improvement of manic symptoms, but to one of the most important treatment goals for manic patients; the attainment of an equilibrium in symptomology including mood stability, and progress towards remission.

The claim 'Towards Equilibrium Fast' left the reader in no doubt that AstraZeneca referred to a fast start in **progress** toward a treatment goal (in this case, remission). Symptomatic remission required a significant decrease in manic symptoms. That significant reduction in symptoms was seen rapidly (at day 4, $p<0.021$ versus placebo) with Seroquel (Jones and Huizar).

A significant symptomatic improvement at day 4 referred to by Jones and Huizar was in line with the response seen with other atypical antipsychotics when compared with placebo. Risperidone had been shown to significantly improve mania symptoms versus placebo at 3 days, and olanzapine had been demonstrated to significantly improve mania symptoms versus placebo at day 7. Therefore separation from placebo for the other atypical antipsychotics took place around days 3-7 and so AstraZeneca was justified in using the word 'fast'. Even though Seroquel was being titrated up to reach the minimum optimal dose by day 4, a significant difference versus placebo was seen, even at this early stage.

With reference to the claim that olanzapine produced a greater improvement than valproate after 2 days of treatment, this statistically significant difference was only seen at day 2 and not day 1 and day 3 through to 7. A 'one-off' difference seen at one timepoint out of seven in the first week was not unexpected, but one

significant time-point should not be used to signify onset of action, when no difference was demonstrated at following time-points. Another trial assessing valproate versus olanzapine for mania showed the treatments to be of similar efficacy at all timepoints.

PANEL RULING

The Panel noted that the claim 'Towards Equilibrium Fast' appeared on a page which discussed Seroquel's new indication in mania associated with bipolar disorder. The Panel did not accept Lilly's assertion that this was a claim for a fast onset of action. Equilibrium was defined as a well-balanced state of mind or feeling, equanimity (ref: The New Shorter Oxford English Dictionary 1993). Within the context of the disease, mania associated with bipolar disorder, the Panel considered that 'Towards Equilibrium Fast' referred to the reduction of manic symptoms. The Panel did not consider that the Seroquel dose titration regimen at days 1-4 in itself meant that Seroquel did not move a patient towards equilibrium fast. The Panel noted that Jones and Huizar showed that Seroquel significantly reduced the severity of mania as measured by the Young Mania Rating Scale (YMRS) at day 4, $p<0.05$ versus placebo. The statistically significant difference between the two, in favour of Seroquel, was maintained until the end of the trial at day 84.

The Panel noted the parties' submissions about the onset of action of olanzapine (Tohen *et al* 2002) but did not consider that the claim was directly or implicitly comparative.

Given Jones and Huizar the Panel did not consider the claim 'Towards Equilibrium Fast' unreasonable or misleading as alleged. No breach of Clause 7.2 was ruled.

B Leavepiece ref A45241

Claims: 'Lasting improvement in mania symptoms' and 'Fast and lasting improvement in mania symptoms over three months'

These claims appeared on page 3 of the leavepiece which discussed the use of Seroquel in mania associated with bipolar disorder. 'Lasting improvement in mania symptoms' appeared as the page heading, above the bullet point 'Fast and lasting improvement in mania symptoms over three months' which was referenced to Jones and Huizar. A graph on the page depicted data from Jones and Huizer showing the mean change from baseline in the YMRS over 84 days of Seroquel monotherapy versus placebo.

COMPLAINT

Lilly stated that the claims at issue referred to the long-term benefits of Seroquel monotherapy. Lilly stated that Seroquel was indicated for manic episodes associated with bipolar disorder and was not licensed for relapse prevention in bipolar disorder. This claim was therefore a breach of Clause 3.2.

RESPONSE

AstraZeneca stated that the Seroquel SPC Section 4.1 stated that Seroquel was licensed for the treatment of manic episodes associated with bipolar disorder.

The claim, 'lasting improvement of mania symptoms' was always qualified with 'over three months' and as used in all AstraZeneca material, was not misleading.

The claim was wholly based on the effect of Seroquel treating the symptoms of manic episodes (mania symptoms) and this claim was supported by data that looked at the change in mania symptoms over a 3-month period. These data demonstrated that Seroquel led to an improvement of mania symptoms, the onset of which was fast (by day 4) and which continued out to 3 months. Manic episodes could last up to 3 months so it was important and consistent with the licensed indication to measure symptomatic changes up to this clinically relevant endpoint. Relapse prevention was not mentioned explicitly or by implication; relapse was not measured as part of the trial, so no claim could be made concerning this.

The claim 'Fast and lasting improvement in mania symptoms over three months' was in line with the licensed indications for Seroquel and was therefore not a breach of Clause 3.2.

PANEL RULING

The Panel noted that Seroquel was indicated, *inter alia*, for the treatment of manic episodes associated with bipolar disorder. The Panel noted Lilly's allegation that 'Lasting improvement in mania symptoms' and 'Fast and lasting improvement in mania symptoms over three months' were claims for long-term benefits and Seroquel was not licensed for relapse prevention in bipolar disorder.

There was no reference to duration of treatment in the Seroquel SPC. The claim 'Fast and lasting improvement in mania symptoms over three months' was referenced to Jones and Huizar in which the primary objective was to assess the change from baseline in YMRS score at day 21. Secondary endpoints assessed at day 21 and day 84 included the YMRS response rate (≥ 50% reduction in YMRS score) and YMRS remission rate (YMRS score ≤ 12). The data showed that the reduction from baseline for the YMRS score for Seroquel was statistically significantly greater than placebo from day four onwards ($p=0.021$), $p<0.001$ at day 84 (versus placebo). Response and remission rates were also significantly greater with Seroquel than placebo at days 21 and 84 for the YMRS.

The Panel noted that Seroquel was not licensed for prevention of relapse. There was no reference to duration of treatment in the Seroquel SPC. The Panel considered that the claims at issue referred to maintenance of response as measured by the YMRS score. Maintenance of response was not the same as prevention of relapse. The Panel did not consider that either claim implied that Seroquel was indicated for prevention of relapse as alleged. No breach of Clause 3.2 was ruled.

Complaint received **19 March 2004**

Case completed **7 June 2004**

CASE AUTH/1568/3/04

GENERAL PRACTITIONER v BAYER

Market research testing of Avelox edetail

A general practitioner complained about the electronic market research testing of an edetail for Avelox (moxifloxacin) produced by Bayer which appeared on a third party website for the purposes of market research.

Bayer explained that on 1 December it had launched a ten minute, animated edetail. The complaint related to market research on this edetail carried out on behalf of Bayer by a third party via its website.

Bayer explained that GPs were recruited by the market research company to act as GP research consultants. Invitations were sent via email to a sample of GP research consultants inviting them to provide feedback on a chosen edetail. A GP research consultant entered the market research website and signed in using their email address and previously allocated password. Once the GP research consultant had entered the secure website (s)he selected the product that they had been invited to provide feedback on. The GP research consultant viewed their chosen edetail. The GP research consultant was then asked to complete the feedback form and submit it within 14 days. Upon receipt of the completed feedback form the GP research consultant's 'edetail account' was credited with £12.

The complainant noted that on the Avelox edetail it was not possible to link to prescribing information even though claims were made for the product on that page. Within the edetail itself it took two clicks to get to prescribing information. The pdf icon on the pop-up box was not active. The '400mg' text was active and the user was taken to the Avelox.co.uk site. Once there the user was requested to register to that site but there was no prescribing information available on that page. At one point in the edetail it was stated that 'Avelox is the ideal alternative …'. The complainant alleged that the claim was a superlative with no reference.

The complainant noted that there was a link to 'literature'. This gave a range of references but they were not the same in all cases as the references used in the presentation: this was misleading.

The feedback form asked questions about the product and the doctor's attitude to it. The edetail was totally promotional and so it could only be considered market research if it went to a limited sample otherwise it should be considered disguised promotion.

The complainant stated that the doctor was informed in the invitation email and on the site home page that there would be a £12 reward for completing the edetail and submitting the feedback. Assuming this was disguised promotion the £12 was an inducement to take the edetail and exceeded the amount allowable under the Code (about £6 in practice related gift, not cash). If the promotional content was removed the reward would be acceptable.

The complainant pointed out that the feedback form invited the doctor to request samples: it was necessary under the Code to have these signed by the requesting physician and there was no obvious mechanism by which this could take place.

The Panel noted Bayer's submission that the edetail testing was market research. The Code required that such activity must not be disguised promotion. It was acceptable for companies to commission market research to test promotional material. The arrangements for such market research must not contravene the Code. In this case a version of the material in question was already in use and could be accessed from the Avelox website. Bayer had stated that a number of links from the edetail available on the market research website ie prescribing information, literature and the quiz, were not intended to be tested in the market research. In that regard the Panel questioned the value of conducting market research on a less comprehensive version of an edetail than that which was already available on another website. The Panel also noted guidelines – The Legal and Ethical Framework for Healthcare Market Research – produced by the British Healthcare Business Intelligence Association in consultation with the Association of the British Pharmaceutical Industry. The guidelines set out the specific requirements when engaged in detail testing and stated, *inter alia*, that testing promotional material was potentially open to the charge of 'sugging' or 'selling under the guise' of market research. Although there were no hard and fast rules on the sample size to be used for any market research exercise, the sample size must be limited to that necessary to achieve the objectives of the research.

The Panel had not been provided with detailed objectives. It appeared from Bayer's submission that the objective was to ask questions about the product and the GP research consultants' attitude to it. The feedback form asked participants to answer four multiple choice questions upon a 28 page edetail; the questions concerned the length of the presentation, its usefulness, preferred media for promotional material and to identify which one of six statements was the most important message to the reader about Avelox. The Panel noted that 450 GPs had been invited to comment upon a version of the Avelox edetail. In the Panel's view this number of potential respondents was many more than necessary. Given the scale and nature of the exercise the Panel considered that the arrangements amounted to the promotion of Avelox and this was the basis on which it made its rulings. The Panel considered that the market research was disguised promotion and a breach of the Code was ruled.

On the page with the first mention of Avelox it was not possible to link to the prescribing information. Other pages in the edetail itself included prescribing information buttons but these did not work. The Code stated that in the case of promotional material included on the Internet, there must be a clear, prominent statement as to where the

prescribing information could be found. The Code did not require such a statement to accompany the first reference to the product name. Although there was no reference to the prescribing information on the page preceding the edetail such references were provided on other pages and so no breach of the Code was ruled. The Panel noted, however, that although there were references to the prescribing information the links were not active and so the prescribing information could not be accessed. The prescribing information had thus not been provided and a breach of the Code was ruled.

The complainant had referred to a claim 'Avelox is the ideal alternative …'. The claim in question actually read 'Avelox is an ideal alternative …'. The Panel considered that the claim which appeared on the edetail was thus not a superlative as alleged and no breach of the Code was ruled in that regard.

The complainant had stated that the 'literature' link took readers to a list of references which were not always the same as the references cited in the edetail. Bayer had submitted that the literature button, which provided an alphabetical list of all the references used in the presentation, was not intended to be functional as part of the market research. The only requirement under the Code with regard to references was that when promotional material referred to published studies, clear references must be given; this appeared to have been done on the separate pages of the edetail itself. In some cases references had been given where none were required under the Code. The Panel considered that the citation of references within the edetail satisfied the requirements of the Code and were not misleading in that regard.

The Panel noted that once doctors had completed the feedback form their edetail account would be credited with £12. The Code stated that no gift, benefit in kind or pecuniary advantage should be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend or buy any medicine, except that gifts in the form of promotional aids and prizes, whether related to a particular product or a general utility, might be distributed to members of the health professions and to appropriate administrative staff, provided that the gift or prize was inexpensive and relevant to the practice of their profession or employment. Inexpensive was defined as no more than £6 and excluding VAT. The Panel noted that it had ruled that the market research was disguised promotion thus any payment made in association with the study was unacceptable. A breach of the Code was ruled.

The feedback form invited doctors to request starter packs of Avelox. The Code stated that starter packs were small packs of medicine designed for a primary care prescriber to initiate treatment in such circumstances as a call out in the night or in other instances where there might be some undesirable or unavoidable delay in having a prescription dispensed. Antibiotics were listed as appropriate medicines to be provided in starter packs. Starter packs were not the same as samples and were exempt from those requirements of Clause 17 which related to samples. Thus although there was no way a signed request form could be submitted for the starter packs offered none was needed and no breach of the Code was ruled.

A general practitioner complained about the electronic market research testing of an edetail for Avelox (moxifloxacin) produced by Bayer Health Care which appeared on a third party website for the purposes of market research.

Bayer explained that on 1 December 2003 it had launched a ten minute, animated edetail with an accompanying voiceover. The viewer could move forward through the presentation at their own speed and at certain stages a number of questions on the material were asked making the experience an interactive one. Health professionals were invited to log on to the appropriate website page and once registered they were passed through to secure website pages for the start of the presentation. Bayer had an ongoing programme of mailers etc to invite GPs to view the Avelox on-line interactive presentation. The complaint, however, did not refer to this 'live' on-line Avelox presentation but to market research on this presentation carried out on behalf of Bayer by a market research company via its website.

Upon receipt of the complaint, Bayer suspended both the market research and the live on-line Avelox presentation whilst reviewing the specific complaints. The live Avelox on-line presentation was reactivated on 25 March but the market research project, which was virtually complete, was stopped.

Bayer stated that the website was a new market research tool developed by a third party to provide electronic detail follow up research for pharmaceutical companies. The third party had a pool of previously recruited UK doctors who had signed up to provide this follow up service on materials presented by them in return for a fee.

The process of providing the electronic detail follow up market research was as follows: GPs were recruited by the market research company to act as GP research consultants. Invitations were sent via email to a sample of GP research consultants inviting them to provide feedback on a chosen edetail. A copy of the invitation was provided. A GP research consultant entered the market research website and signed in using their email address and previously allocated password. Once the GP research consultant had entered the secure website (s)he selected the product that they had been invited to provide feedback on. The GP research consultant viewed their chosen edetail. The GP research consultant was then asked to complete the feedback form and submit it within 14 days. Upon receipt of the completed feedback form the GP research consultant's 'edetail account' was credited with £12.

COMPLAINT

The complainant noted that on the Avelox edetail in question the first mention of the brand name was not accompanied by a black triangle. Avelox needed this warning as it was a new product. The complainant

further noted that on the same page it was not possible to link to prescribing information even though claims were made for the product on that page.

The complainant stated that within the edetail itself it took two clicks to get to prescribing information. The pdf icon on the pop-up box was not active. The '400mg' text was active and the user was taken to the Avelox.co.uk site. Once there the user was requested to register to that site but there was no prescribing information available on that page.

The complainant noted that at one point in the edetail it was stated that 'Avelox is the ideal alternative …'; there was no reference to this claim so the complainant assumed it to be a statement by Bayer. The complainant alleged that the claim was a superlative with no reference and thus in breach of the Code.

The complainant noted that there was a link to 'literature'. This gave a range of references but they were not the same in all cases as the references used in the presentation: this was misleading.

The complainant noted that the feedback form asked questions about the product and the doctor's attitude to it. The edetail was totally promotional and so it could only be considered market research if it went to a limited sample, otherwise it should be considered disguised promotion.

The complainant stated that the doctor was informed in the invitation email and on the site home page that there would be a £12 reward for completing the edetail and submitting the feedback. Assuming this was disguised promotion the £12 was an inducement to take the edetail and exceeded the amount allowable under the Code (about £6 in practice related gift, not cash). If the promotional content was removed the reward would be acceptable.

The complainant pointed out that the feedback form invited the doctor to request samples: it was necessary under the Code to have these signed by the requesting physician and there was no obvious mechanism by which this could take place.

When writing to Bayer the Authority asked it to respond in relation to Clauses 4.1, 4.6, 7.2, 7.10, 9.1, 10.1, 17.3, 18.1 and 18.2 of the Code.

RESPONSE

Bayer stated that once a GP research consultant opened the home page of the market research company's website (s)he was invited to sign in using a pre-allocated password. The GP research consultant then entered the secure market research site and was able to select the product upon which they wished to provide edetail feedback. It was at this point that the Avelox logo was first displayed (along with a list of approved indications) as one of the edetails available to select. At the time of the Avelox edetail research, the Avelox edetail was the only choice available.

The complainant was correct in that there was no black triangle or link to prescribing information shown at this point. However given that the logo was being used as an identifier in a non-promotional (ie market research) setting Bayer did not consider that provision of prescribing information and a black triangle was necessary.

Bayer stated that while the GP research consultant was viewing the edetail, the active link to the prescribing information was not properly functional. These links were not intended to be tested as part of the market research since Bayer wished to measure the effectiveness of the edetail as a means of communication. As stated above Bayer understood that prescribing information did not need to be provided during market research.

Bayer noted that the complainant's statement with regard to Avelox being the ideal alternative was inaccurate. In fact, the edetail (both written text and voiceover) stated that 'Avelox is **an** [emphasis added] ideal alternative….'. This statement did not contain a superlative.

Bayer stated that as with the black triangle and the prescribing information the literature button (which provided an alphabetical list of all the references used in the presentation) was also not intended to be functional as part of the market research.

The feedback form which the GP research consultants were asked to complete asked questions about the product and their attitude to it. This was the objective of the market research. The research proposal was to obtain responses from a representative sample of UK GPs from the pool of GP research consultants who had previously signed up to the market research company. As indicated earlier, an email was sent to this limited sample of GP research consultants inviting them to provide feedback on the Avelox on-line presentation. The first batch of 200 invitations was sent on 26 February to ascertain the level of response (approximately 50% after 14 days) and then a second batch of 250 invitations was sent on 10 March. The number of GP research consultants who provided feedback was 369 from the 450 invitations sent.

However, notwithstanding the above, Bayer realised while reviewing the complaint that the format of the feedback form could be considered to be in breach of the Code as it contained the Avelox logo at the head of the page and, in addition, the questions on the form made reference to the brand name rather than using alternative wording such as 'the product'.

Bayer stated that GPs were recruited into the pool of market research consultants in the full knowledge that they would be paid a fee of £12 for providing feedback on presentations produced by the pharmaceutical industry. Again, at the time of the invitation to provide feedback on the Avelox edetail, the GP research consultants were reminded that they would only receive this fee on completion of the feedback form (ie not just viewing the Avelox presentation). The £6 limit defined in the Code was not applicable in this instance as this was not a promotional activity.

The complaint referred to the requirement for a signature for samples. Bayer was aware of the requirement for a dated signature for starter packs and a process was in place for the 'live' Avelox on-line

presentation for handling such requests (using an emailed 'Faxback' form for the doctor to sign and return).

Bayer explained that whilst reviewing the market research process a further issue came to light which it brought to the Authority's attention:

At the end of the 'live' on-line Avelox presentation the viewer was asked a number of questions:

– May we (Bayer) contact them again?

– Would they like to order starter packs?

– Would they like to send a comment?

These same questions also appeared on pages at the back of the Avelox presentation shown as part of the market research between 26 February and 5 March although they were not being tested as part of the market research. However, in the early days of the research a number of technical difficulties were experienced by GP research consultants using the market research website (the same difficulties referred to above). Because of these difficulties, on 5 March the market research company and the German agency hosting the 'live' Avelox on-line presentation made a number of alterations to the computer program controlling the presentation and feedback form. One of these changes was to shorten the market research presentation by removing the final 6 pages. During this process the German agency advised the market research company to incorporate more questions on to the market research feedback form. This revised feedback form was then used to collate feedback from the GP research consultants from 5 to 19 March.

Bayer accepted that the three questions listed above (which could legitimately be asked of GPs viewing the 'live' Avelox on-line presentation) should not have been asked of the GP research consultants in the market research. Although modification of the feedback form was carried out without reference back to Bayer it accepted full responsibility for it. No response had been made by the company to any of these questions and no starter packs had been dispatched even if they were requested.

In summary, the complainant would have been well aware that he was viewing the Avelox edetail in his capacity as a GP research consultant and within the confines of market research. The GP research consultants had been recruited by the market research organisation to provide this service in return for a fee and they were reminded of this fact at the time that they were invited to provide feedback on the Avelox edetail.

However, Bayer acknowledged there was a shortcoming in this market research. The design of the feedback form contained elements which were inappropriate in the context of market research and might be considered in breach of the Code. In the light of this shortcoming the company's internal processes were under review to ensure that there was no possibility of a future recurrence.

PANEL RULING

The Panel noted that the Avelox edetail in question was available on the website of a market research company on behalf of Bayer. It was an established principle under the Code that activities carried out with the authority of a pharmaceutical company were the responsibility of that pharmaceutical company even if a third party was involved. Bayer was thus responsible for the market research testing of its Avelox edetail aid.

The Panel noted Bayer's submission that the edetail testing was market research. Clause 10.2 of the Code required that such activity must not be disguised promotion. It was acceptable for companies to commission market research to test promotional material. The arrangements for such market research must not contravene the Code. In this case a version of the material in question was already in use and could be accessed from the Avelox website. The Panel noted that Bayer had stated that a number of links from the edetail available on the market research website ie prescribing information, literature and the quiz, were not intended to be tested in the market research. In that regard the Panel questioned the value of conducting market research on a less comprehensive version of an edetail than that which was already available on another website. The Panel also noted the supplementary information to Clause 10.2 drew attention to guidelines – The Legal and Ethical Framework for Healthcare Market Research – produced by the British Healthcare Business Intelligence Association in consultation with the Association of the British Pharmaceutical Industry. Section 8 of the guidelines set out the specific requirements when engaged in detail testing and stated, *inter alia*, that testing promotional material was potentially open to the charge of 'sugging' or 'selling under the guise' of market research. Section 2.1 of the guidelines stated that although there were no hard and fast rules on the sample size to be used for any market research exercise, the sample size must be limited to that necessary to achieve the objectives of the research.

The Panel had not been provided with detailed objectives. It appeared from Bayer's submission that the objective was to ask questions about the product and the GP research consultants' attitude to it. The feedback form asked participants to answer four multiple choice questions upon a 28 page edetail; the questions concerned the length of the presentation, its usefulness, preferred media for promotional material and to identify which one of six statements was the most important message to the reader about Avelox. The Panel noted that 450 GPs had been invited to comment upon a version of the Avelox edetail. In the Panel's view this number of potential respondents was many more than necessary. Given the scale and nature of the exercise the Panel considered that the arrangements amounted to the promotion of Avelox and this was the basis on which it made its rulings. The Panel considered that the market research was disguised promotion. A breach of Clause 10.2 was ruled.

The Panel noted that the first use of the brand name Avelox was on a page of the market research website which preceded the edetail itself. The brand name appeared in logo type and beneath it was the name of the medicine, its pharmacological class and uses. The

Panel noted that the brand name was not accompanied by an inverted black triangle. Although use of the black triangle was not a requirement of the Code the Panel requested that Bayer be reminded of the agreement which existed between the Committee on Safety of Medicines and the ABPI on the use of the symbol as set out in the supplementary information to Clause 4.3.

The Panel noted that on the page with the first mention of Avelox it was not possible to link to the prescribing information. Other pages in the edetail itself included prescribing information buttons but these did not work. Clause 4.6 of the Code stated that in the case of promotional material included on the Internet, there must be a clear, prominent statement as to where the prescribing information could be found. The Code did not require such a statement to accompany the first reference to the product name. Although there was no reference to the prescribing information on the page preceding the edetail such references were provided on other pages and so no breach of Clause 4.6 was ruled. The Panel noted, however, that although there were references to the prescribing information the links were not active and so the prescribing information could not be accessed. The prescribing information as required by Clause 4.1 of the Code had thus not been provided and a breach of that Clause was ruled.

The Panel noted that the complainant had referred to a claim 'Avelox is the ideal alternative …'. The claim in question actually read 'Avelox is an ideal alternative …'. The Panel considered that the claim which appeared on the edetail was thus not a superlative as alleged and no breach of Clause 7.10 was ruled.

The Panel noted that the complainant had stated that the 'literature' link took readers to a list of references which were not always the same as the references cited in the edetail. Bayer had submitted that the literature button, which provided an alphabetical list of all the references used in the presentation, was not intended to be functional as part of the market research. The Panel noted that the only requirement, however, under the Code with regard to references was that when promotional material referred to published studies, clear references must be given; this appeared to have been done on the separate pages of the edetail itself. In some cases references had been given where none were required under the Code. The Panel considered that the citation of references within the edetail satisfied the requirements of the Code and were not misleading in that regard. No breach of Clause 7.2 was ruled.

The Panel noted that once doctors had completed the feedback form their edetail account would be credited with £12. Clause 18.1 of the Code stated that no gift, benefit in kind or pecuniary advantage should be offered or given to members of the health professions or to administrative staff as an inducement to prescribe, supply, administer, recommend or buy any medicine, subject to the provisions of Clause 18.2.

Clause 18.2 of the Code stated that gifts in the form of promotional aids and prizes, whether related to a particular product or a general utility, might be distributed to members of the health professions and to appropriate administrative staff, provided that the gift or prize was inexpensive and relevant to the practice of their profession or employment. Inexpensive was defined in the supplementary information as no more than £6, excluding VAT. The Panel noted that it had ruled that the market research was disguised promotion thus any payment made in association with the study was in breach of Clause 18.1 of the Code. The Panel thus ruled a breach of that clause.

The feedback form invited doctors to request starter packs of Avelox. The supplementary information to Clause 17 stated that starter packs were small packs of medicine designed for a primary care prescriber to initiate treatment in such circumstances as a call out in the night or in other instances where there might be some undesirable or unavoidable delay in having a prescription dispensed. Antibiotics were listed as appropriate medicines to be provided in starter packs. Starter packs were not the same as samples and were exempt from those requirements of Clause 17 which related to samples. Thus although there was no way a signed request form could be submitted for the starter packs offered none was needed. The Panel ruled no breach of Clause 17.3 of the Code.

During its consideration of this case the Panel noted that the Avelox Quick Competition comprised three questions the answers to which could be found in the preceding edetail. In the Panel's view such a competition was not a *bona fide* test of skill as required by Clause 18 of the Code. Any prizes offered in association with such a competition would thus be in breach of the Code. The Panel requested that Bayer be advised of its concerns in this regard.

The Panel also noted that at the end of the edetail participants were thanked for taking part and told that the first 500 who successfully completed the presentation would receive a free diagnostic lamp. There was no indication as to the cost of the lamp but the Panel requested that Bayer be reminded of the £6 excluding VAT limit on promotional gifts and prizes. The Panel was also concerned that the provision of the lamp might be seen as or used as an inducement to read the promotional material. Such use was not acceptable under the Code as Clause 15.3 stated that no fee should be paid or offered for the grant of an interview. In the Panel's view the same principle applied to edetails ie health professionals should not be offered an incentive to view them. The Panel noted that there was no evidence that this had happened but nevertheless requested that Bayer be advised of its concerns.

Complaint received **22 March 2004**

Case completed **4 June 2004**

CASE AUTH/1569/3/04

HOSPITAL CHIEF PHARMACIST v ASTRAZENECA

Nexium IV letter

A hospital chief pharmacist complained about a letter he had received from AstraZeneca which had announced the launch of Nexium IV (intravenous esomeprazole). The complainant alleged that the claim 'esomeprazole 40mg IV has a higher bioavailability than omeprazole 40mg IV' was incorrect according to the definitions of bioavailability, and would suggest to the less informed reader that Nexium had some form of added value as a result. Bioavailability was defined as the percentage of an administered medicine that reached the systemic circulation and for all preparations depended on the percentage adsorbed; for intravenous products, bioavailability was always 100%. Therefore, by definition, esomeprazole IV and omeprazole IV would have identical bioavailability.

The Panel noted that bioavailability was understood to be the extent and the rate at which a substance or its active moiety was delivered from a pharmaceutical form and became available in the general circulation. It must follow, therefore, that the bioavailability of IV preparations was 100%. The claim 'esomeprazole 40mg IV has a higher bioavailability than omeprazole 40mg IV' was therefore not in accordance with the generally understood definition of bioavailability as accepted by AstraZeneca. The claim was thus misleading in that regard and could not be substantiated. Breaches of the Code were ruled.

A hospital chief pharmacist complained about a letter he had received from AstraZeneca UK Limited which had announced the launch of Nexium IV (intravenous esomeprazole).

COMPLAINT

The complainant alleged that the claim 'esomeprazole 40mg IV has a higher bioavailability than omeprazole 40mg IV', which appeared in the summary section of the letter, was incorrect according to the definitions of bioavailability and would suggest to the less informed reader that Nexium had some form of added value as a result. Bioavailability was defined as the percentage of an administered medicine that reached the systemic circulation and for all preparations depended on the percentage adsorbed; for intravenous products, bioavailability was always 100%. Therefore, by definition, esomeprazole IV and omeprazole IV would have identical bioavailability.

The complainant had contacted AstraZeneca and had spoken to the person who had signed the letter who, in hindsight, agreed that a mistake had been made. The complainant did not think that AstraZeneca was prepared to admit this mistake to a wider audience.

RESPONSE

AstraZeneca stated that the letter in question was sent to pharmaceutical advisers on 15 March. Another more detailed announcement was sent out to medicines information pharmacists. The complainant had first contacted the company with his concerns about the use of the term 'bioavailability' on 24 March and the company had replied the next day and assured him that it would look into the matter.

AstraZeneca explained that oral esomeprazole, the s-isomer of omeprazole, was known to have a higher bioavailability than oral omeprazole; studies looking into this had measured area under the curve (AUC) values (Andersson *et al* 2001a; Andersson *et al* 2001b). The definition of bioavailability was taken to mean the amount of medicine absorbed into the bloodstream and available to be biologically active. As such, AUC and bioavailability were terms used interchangeably for the oral formulation.

A similar study was performed with IV formulations of Nexium 40mg and omeprazole 40mg (AstraZeneca data on file). AUC values demonstrated significant superiority for Nexium vs omeprazole, as discussed in the letter to medicines information pharmacists. Because this study showed that after metabolic processes, more esomeprazole was available in the bloodstream than omeprazole after day 1 and day 5, the summary of this study stated that 'esomeprazole 40mg IV has a higher bioavailability than omeprazole 40mg IV'.

Bioavailability in this study was defined as the amount of medicine available in the bloodstream after metabolic processes at equal time points after initial bolus infusions of the same doses of both respective IV formulations. AUC measurements of both medicines after initial bolus infusions at designated time-points were used as the surrogate measure for their respective bioavailabilities.

As discussed with the complainant this was an error in the use of the term 'bioavailability' which was not in accordance with the generally accepted pharmacokinetic definition. AstraZeneca had not intended to mislead or exaggerate the data. The company had acknowledged that an error was made. Should the Panel rule a breach of the Code the company would of course take the necessary remedial action.

PANEL RULING

The Panel noted that bioavailability was understood to be the extent and the rate at which a substance or its active moiety was delivered from a pharmaceutical form and became available in the general circulation. It must follow, therefore, that the bioavailability of IV preparations was 100%. The claim 'esomeprazole 40mg IV has a higher bioavailability than omeprazole 40mg IV' was therefore not in accordance with the generally understood definition of bioavailability as accepted by AstraZeneca. The claim was thus misleading in that regard and could not be substantiated. Breaches of Clauses 7.2, 7.3 and 7.5 were ruled.

Complaint received **29 March 2004**

Case completed **12 May 2004**

GENERAL PRACTITIONER/COMMITTEE OF THE ROYAL COLLEGE OF GENERAL PRACTITIONERS v SCHERING HEALTH CARE

Yasmin market research

A general practitioner complained, via a committee of the Royal College of General Practitioners, about market research on Yasmin commissioned by Schering Health Care. The complainant referred to a facsimile sent by a market research company which invited recipients to partake in patient feedback on Yasmin. It was addressed to a person at the complainant's practice and referred to their recent telephone conversation with the market research company.

The complainant was concerned that the facsimile was unsolicited. It concerned the recruitment of patients using Yasmin, by the GPs in the practice and offered a case 'incentive' for both GP and patient. The facsimile then assured the reader that the company adhered to the market research code of conduct, implying that such recruitment had been ethically vetted.

The committee of the Royal College of General Practitioners stated that it was difficult to know whether the market research in question was disguised promotion when the practice was not provided with a copy of the questionnaire or of the information provided for patients.

The Panel noted Schering Health Care's submission that the facsimile at issue was an invitation to take part in market research. The Code required that such activity must not be disguised promotion. The Panel also noted the Legal and Ethical Framework for Healthcare Market Research – produced by the British Healthcare Business Intelligence Association in consultation with the Association of the British Pharmaceutical Industry. Section 2.1 of the guidelines stated, *inter alia*, that appropriate compensation should be made to respondents for their time and that at no time should incentives be increased or inducements given which could influence respondents' opinions. Section 12 stated that in situations where respondents were lay members of the public incentives might be provided at a level that was appropriate as a reasonable token of appreciation for their participation.

The Panel noted that the facsimile at issue was headed 'Patient feedback – Yasmin Contraceptive Pill' and explained that the market research company wished to undertake market research on behalf of Schering Health Care to assess patient experience of Yasmin. The patient profile was described and the letter stated that 'We are willing to offer incentives of £10 to each participating patient together with a £15 incentive to the provider of the contact details for each and every questionnaire completed'. The questionnaire would take less than 5 minutes.

The Panel examined the documentation for the market research. A letter to participating GPs explained that the purpose of the research was to assess patient experience of Yasmin. Doctors were asked to send an introductory letter, provided by the market research company to women who were taking Yasmin and had done so for at least three months, or who were first prescribed Yasmin more than six months ago and who might or might not still be on it.

Patients receiving the introductory letters were invited to telephone the market research company to complete a questionnaire. The questionnaires asked women about how long they had taken Yasmin, its beneficial effects, comparison with previous oral contraceptives and, if patients had ceased use, questions about present contraceptive method.

The Panel considered that the facsimile was an invitation to take part in *bona fide* market research. The purpose of the market research was set out clearly in the facsimile. The only requirement under the Code was that such research was not a disguised promotional activity. The Panel did not consider that the activity constituted disguised promotion. High standards had been maintained. No breaches of the Code were ruled.

The Code provided that *inter alia*, facsimile could not be used for a promotional purpose without the prior permission of the recipient. It was unclear on the evidence before the Panel whether the market research company had spoken to somebody at the surgery before sending the facsimile. Nonetheless, given its ruling that the facsimile was not disguised promotion such permission, whilst good practice, was not required in any event. No breach of the Code was ruled.

A general practitioner complained, via a committee of the Royal College of General Practitioners, about market research on Yasmin commissioned by Schering Health Care Limited. The complainant referred to a facsimile sent by a market research company which invited recipients to partake in patient feedback on Yasmin. It was addressed to a person at the complainant's practice and referred to their recent telephone conversation.

COMPLAINT

The complainant was concerned that her practice manager had received the facsimile, canvassing help with patient feedback on Yasmin. Contrary to the detail on the facsimile, it had been unsolicited and its arrival at the practice was the first notice the practice manager had received about the project.

The facsimile concerned the recruitment of patients using Yasmin, by the GPs in the practice and offered a case 'incentive' for both GP and patient. The facsimile then assured the reader that the company adhered to the market research code of conduct, implying that such recruitment had been ethically vetted.

The complainant stated that whatever market research code applied, offering case incentives was one of the points to be considered and approved by a research

ethics committee before NHS patients could be recruited to the study. When the complainant contacted the market research company to ask which ethics committee had approved this study, it was very surprised at her request and promised to get back to her with the information that same day. However, it had not done so.

The covering letter from a committee of the Royal College of General Practitioners stated that it was difficult to know whether the market research in question was disguised promotion when the practice was not provided with a copy of the questionnaire or of the information provided for patients.

When writing to Schering Health Care the Authority asked it to respond in relation to Clauses 9.1, 9.9 and 10.2 of the Code.

RESPONSE

Schering Health Care stated that the facsimile message transmitted to the complainant stated clearly that the intention was to assess patient experience of Yasmin. It made no product claims and explicitly concerned only previous prescriptions of Yasmin. It did not seek, in any way, to either promote the further use of Yasmin or induce future prescription of it and so in the company's view could not be considered as disguised promotion. Schering Health Care submitted that this communication was not promotional in nature and so was not subject to the requirements of Clauses 9.9 and 10.2 of the Code.

The complainant had suggested that the market research code of conduct might have been breached in respect of a need to ethically vet such patient recruitment. Schering Health Care stated that in its opinion such a questionnaire survey of patient experience did not meet the description of a study in terms of either an interventional trial or an observational surveillance project. The purpose was clearly described as market research and was thus covered by the specific requirements outlined in the guidance from the British Healthcare Business Intelligence Association. This allowed firstly the recruitment of patients for participation in market research via a health professional and secondly for an appropriate incentive, 'as a reasonable token of appreciation for their participation'. There was no requirement for ethical approval of market research of this nature. In the circumstances, Schering Health Care did not consider that there had been any breach of Clause 9.1.

The market research company initially measured interest from the GP by telephone and then by facsimile letter, as received by the complainant. If the recipient was interested in participating, they were then sent a further letter, together with a supply of introductory letters for despatch to potential patients which invited them to respond by calling the telephone number provided.

When contacted by the patient, the market research company would complete one of the two possible questionnaires depending upon their use of Yasmin. Patient anonymity was preserved as no more detail than the number of questionnaires successfully completed was passed back to the initiating GP. Allowance was made for some restriction of numbers in each practice contacted, with the proviso explained in the patient letter that they might not be able to participate if the maximum return had already been achieved.

The criterion for payment to the patient was the satisfactory completion of a questionnaire. For payment in the case of the GP, the criterion was completion of a questionnaire by a patient referred by them.

All materials used in the survey had been examined by Schering Health Care to ensure their compliance with the Code.

Schering Health Care noted that as it did not know who the complainant was it had been unable to identify any specific details of the contact made in this case. It was not the market research company's practice to send out facsimiles without a prior contact by telephone, usually to the practice manager concerned, since the response rate was known to be very poor. The market research company maintained a log of all outbound calls. Unfortunately it did not record in-coming calls and it was therefore unable to offer any further explanation of why there was apparently a failure to respond with an answer to the complainant's enquiry regarding the need for ethical approval.

PANEL RULING

The Panel noted that the facsimile at issue had been sent by a company carrying out market research on behalf of Schering Health Care. It was an established principle under the Code that pharmaceutical companies were responsible for activities carried out by third parties with their authority. Schering Health Care was thus responsible for the market research activity at issue.

The Panel noted Schering Health Care's submission that the facsimile at issue was an invitation to take part in market research. Clause 10.2 of the Code required that such activity must not be disguised promotion. The Panel also noted the supplementary information to Clause 10.2 drew attention to guidelines – The Legal and Ethical Framework for Healthcare Market Research – produced by the British Healthcare Business Intelligence Association in consultation with the Association of the British Pharmaceutical Industry. Section 2.1 of the guidelines stated, *inter alia*, that appropriate compensation should be made to respondents for their time and that at no time should incentives be increased or inducements given which could influence respondents' opinions. Section 12 stated that in situations where respondents were lay members of the public incentives might be provided at a level that was appropriate as a reasonable token of appreciation for their participation.

The Panel noted that the facsimile at issue was headed 'Patient feedback – Yasmin Contraceptive Pill' and explained that the market research company wished to undertake market research on behalf of Schering Health Care to assess patient experience of

Yasmin. The patient profile was described and the letter stated that 'We are willing to offer incentives of £10 to each participating patient together with a £15 incentive to the provider of the contact details for each and every questionnaire completed'. The questionnaire would take less than 5 minutes.

The Panel examined the documentation for the market research. A letter to participating GPs explained that the purpose of the research was to assess patient experience of Yasmin. Doctors were asked to send an introductory letter, provided by the market research company to women who were taking Yasmin and had done so for at least three months, or who were first prescribed Yasmin more than six months ago and who might or might not still be on it. Patients receiving the introductory letters were invited to telephone the market research company to complete a questionnaire. The questionnaires asked women about how long they had taken Yasmin, its beneficial effects, comparison with previous oral contraceptives and, if patients had ceased use, questions about present contraceptive method.

The Panel considered that the facsimile was an invitation to take part in *bona fide* market research. The purpose of the market research was set out clearly in the facsimile. The only requirement under the Code was that such research was not a disguised promotional activity as set out in Clause 10.2. The Panel did not consider that the activity constituted disguised promotion. High standards had been maintained. No breaches of Clauses 10.2 and 9.1 were ruled.

Clause 9.9 provided that *inter alia* facsimile could not be used for a promotional purpose without the prior permission of the recipient. It was unclear on the evidence before the Panel whether the market research company had spoken to somebody at the surgery before sending the facsimile. Nonetheless, given its ruling that the facsimile was not disguised promotion such permission, whilst good practice, was not required in any event. No breach of Clause 9.9 was ruled.

Complaint received **5 April 2004**

Case completed **8 June 2004**

CASE AUTH/1575/4/04

GLAXOSMITHKLINE v AVENTIS PASTEUR MSD

Inflexal V leavepiece

GlaxoSmithKline complained about a leavepiece entitled 'About to order your flu vaccine for next season?' for Inflexal V (virosomal influenza vaccine) issued by Aventis Pasteur MSD. Readers were informed that although standard influenza vaccines provided significant public health benefits – as patients aged, their response to these vaccines might decline. The leavepiece urged readers to target their over 75s with Inflexal V and referred to a clinical study in the elderly.

The claim 'Some published studies have shown Inflexal V to offer greater seroprotection in the elderly than standard flu vaccines' was referenced to Conne *et al* (1997), Gluck *et al* (1994) and Baldo *et al* (2001). GlaxoSmithKline noted that the claim was based on studies that included 487 patients, but failed to reference Ruf *et al* (2003) which involved 827 adults aged over 60 years that compared the immunogenicity of Inflexal V to standard influenza vaccines (Fluarix, GlaxoSmithKline and Fluad, Chiron-Behring). Inflexal V offered no advantage in terms of immunogenicity or reactogenicity when compared to standard influenza vaccines (no statistical analysis was performed).

The leavepiece at issue was dated October 2003; Ruf *et al* was presented in September 2003 and therefore should have been included. GlaxoSmithKline alleged that the claim was misleading as it did not reflect all of the available evidence.

The Panel noted that the claim 'Some published studies have shown Inflexal V to offer greater seroprotection in the elderly than standard flu vaccines' was true to the extent that two small studies (Conne *et al* (n=72) and Gluck *et al* (n=126)) had shown advantages for Inflexal V compared with standard vaccines; however two much larger ones (Baldo *et al* (n=285) and Ruf *et al* (n=827)) had not. Given the relative size of the studies the Panel considered that the balance of the evidence was such that there was no advantage for Inflexal V in the elderly compared with standard flu vaccines. The claim thus did not reflect all of the evidence clearly and was misleading in that regard and a breach of the Code was ruled.

GlaxoSmithKline stated that the claim 'As patients age, their response to [standard flu] vaccines may decline. Target your over 75s with Inflexal V' inferred that Inflexal V offered greater seroprotection compared to standard influenza vaccines specifically in elderly patients aged over 75 years. However the cited studies (Conne *et al*, Gluck *et al* and Baldo *et al*) had all been conducted in adults over the age of 60 and not specifically in those aged over 75.

The leavepiece also included a graph which depicted the results of Conne *et al* where the mean age of the subjects in the study was stated as being 80 years. However the age range of the patients in this study was 61-98 years. This misled the prescriber to believe these studies had been conducted in patients aged over 75 and GlaxoSmithKline alleged a breach of the Code.

The Panel considered that the inside pages of the leavepiece would be read as a double page spread. On the left-hand side was the claim in question 'As patients age, their response to [standard vaccines] may decline. Target your over 75s with Inflexal V' while on the right-hand side was a bar chart

depicting the results of Conne *et al*. The bar chart was headed 'Proportion of elderly patients seroprotected against the three flu strains contained in the vaccines'. The results shown were 68% for Inflexal V and 38% for a subunit vaccine (p=0.01). A footnote to the bar chart stated that the mean age of the 72 patients was 80 years. Given the claim on the left-hand page and the footnote to the bar chart the Panel considered that many readers would assume that the studies referenced in the leavepiece related only to patients aged over 75 which was not so. The Panel considered that the leavepiece was misleading and breaches of the Code were ruled.

GlaxoSmithKline UK Ltd complained about the promotion of Inflexal V (virosomal influenza vaccine) by Aventis Pasteur MSD Ltd. The material at issue was a four page leavepiece (ref 4089) entitled 'About to order your flu vaccine for next season?'. Readers were informed that although standard influenza vaccines provided significant public health benefits – as patients aged, their response to these vaccines might decline. The leavepiece urged readers to target their over 75s with Inflexal V and then referred to a clinical study in the elderly.

1 Claim 'Some published studies have shown Inflexal V to offer greater seroprotection in the elderly than standard flu vaccines'

This claim was referenced to Conne *et al* (1997), Gluck *et al* (1994) and Baldo *et al* (2001).

COMPLAINT

GlaxoSmithKline noted that the claim was based on studies that included 487 patients, but failed to reference an open, multicentre, randomised study by Ruf *et al* (2003) which involved 827 adults aged over 60 years that compared the immunogenicity of Inflexal V to standard influenza vaccines (Fluarix, GlaxoSmithKline and Fluad, Chiron-Behring). The results from this study were presented in an abstract and poster at an international conference in September 2003 and GlaxoSmithKline provided them in the form of a table.

Inflexal V offered no advantage in terms of immunogenicity or reactogenicity when compared to standard influenza vaccines (no statistical analysis was performed).

The leavepiece at issue was dated October 2003; Ruf *et al* was presented in September 2003 and therefore should have been included.

GlaxoSmithKline alleged that the claim was misleading, in breach of Clause 7.2, as it did not reflect all of the available evidence.

GlaxoSmithKline noted that it had written to Aventis Pasteur MSD which acknowledged that Ruf *et al* should be referenced but did not agree to amend the claim to reflect the balance of evidence or withdraw the leavepiece.

RESPONSE

Aventis Pasteur MSD noted that in its response to GlaxoSmithKline it had stated that the abstract by Ruf *et al* was still under assessment when the leavepiece at issue was produced. In particular, Aventis Pasteur MSD had some legitimate concerns regarding Ruf *et al* which it wished to resolve before quoting the abstract and in that regard the company provided a copy of an email it had written seeking clarification of some of the data. To date no response has been received. Although Ruf *et al* was a GlaxoSmithKline sponsored study, GlaxoSmithKline had been unable to assist in resolving Aventis Pasteur MSD's queries.

Aventis Pasteur MSD submitted that the above explained why Ruf *et al* was not cited in the leavepiece. However even if reference had been made to Ruf *et al*, this would not have altered the claim that 'Some published studies have shown Inflexal V to offer greater seroprotection in the elderly than standard influenza vaccines'. The word 'some' in this context implied that a proportion of published studies had shown Inflexal V to offer greater seroprotection in the elderly than standard influenza vaccines, as opposed to the fact that all studies supported this conclusion. It was clear that this was the intended meaning of the leavepiece because two of the cited papers supported that conclusion (Conne *et al* and Gluck *et al*) and the other (Baldo *et al*) did not. Thus, Aventis Pasteur MSD considered that the claim at issue did not breach Clause 7.2 of the Code and that if this were supported by the existing three references plus Ruf *et al* it would still not be in breach.

Aventis Pasteur MSD stated that it did not accede to GlaxoSmithKline's request to withdraw the leavepiece because the claim was necessarily and obviously limited by use of the word 'some' ('some studies…' as opposed to just 'studies…' or 'all studies…'). The claim was not misleading as it currently stood, referenced to studies both for and against the claim. The company's ability to make the basic claim pertaining to 'some studies' (but not all) would be unaffected by the inclusion of Ruf *et al* and since the large scale selling of influenza vaccines effectively ended in March each year (orders taken for delivery in the following October) the leavepiece was at the end of its lifespan, after which the influenza campaign and any materials for the forthcoming season would be reviewed in any case.

Aventis Pasteur MSD did not consider that the leavepiece at issue was in breach of Clause 7.2 of the Code as alleged.

PANEL RULING

The Panel noted that the claim 'Some published studies have shown Inflexal V to offer greater seroprotection in the elderly than standard flu vaccines' was true to the extent that two small studies (Conne *et al* (n=72) and Gluck *et al* (n=126)) had shown advantages for Inflexal V compared with standard vaccines; however two much larger ones (Baldo *et al* (n=285) and Ruf *et al* (n=827)) had not. Given the relative size of the studies the Panel considered that the balance of the evidence was such that there was no advantage for Inflexal V in the elderly compared with standard flu vaccines. The claim thus did not reflect all of the evidence clearly and was misleading in that regard. A breach of Clause 7.2 was ruled.

2 Claim 'As patients age, their response to [standard flu] vaccines may decline. Target your over 75s with Inflexal V'

COMPLAINT

GlaxoSmithKline stated that this claim inferred that Inflexal V offered greater seroprotection compared to standard influenza vaccines specifically in elderly patients aged over 75 years. However the cited studies (Conne *et al*, Gluck *et al* and Baldo *et al*) had all been conducted in adults over the age of 60 and not specifically in those aged over 75.

The leavepiece also included a graph which depicted the results of Conne *et al* where the mean age of the subjects in the study was stated as being 80 years. However the age range of the patients in this study was 61-98 years.

This misled the prescriber to believe these studies had been conducted in patients aged over 75. GlaxoSmithKline alleged breaches of Clauses 7.2 and 7.4.

GlaxoSmithKline stated that it raised this point with Aventis Pasteur MSD which stated that the decision to recommend Inflexal V for use in patients aged over 75 was a commercial one. Additionally Aventis Pasteur MSD stated that this recommendation was generally in line with the Department of Health's update on adult immunization, issued 8 August 2003 which stated 'Studies have shown that [Inflexal V] may be more immunogenic in older age groups (80+ years) but whether this results in greater protection is not known'. This update was sent to health professionals before Ruf *et al* had been presented in September 2003. GlaxoSmithKline stated that it had subsequently notified the Department of Health of this publication and it had informed GlaxoSmithKline that it would not be recommending one particular influenza vaccine over others in the future in the absence of any new data being published.

RESPONSE

Aventis Pasteur MSD did not agree that health professionals would be misled by the claim; they would not take it to mean that studies had been conducted exclusively in patients aged over 75 years. The claim was made purely for commercial reasons and to guide customers as to in what circumstances Inflexal V might be seriously considered for some patients. This was broadly in line with the Department of Health update issued last August at the beginning of the last influenza vaccination season. Aventis Pasteur MSD further submitted that its position on Inflexal V for the over 75s fell totally within the summary of product characteristics (SPC) for the product. The company did not consider that the words 'Target your over 75s with Inflexal V' were juxtaposed in the leavepiece in a way which would mislead the prescriber to believe that the data from Conne *et al* related solely to patients aged over 75.

Aventis Pasteur MSD did not accept that the leavepiece was in breach of Clauses 7.2 or 7.4 of the Code as alleged. The company noted that for entirely separate commercial reasons relating to the end of this year's influenza vaccine selling season, the leavepiece had now been formally recalled at the end of its intended period of circulation.

PANEL RULING

The Panel considered that the inside pages of the leavepiece would be read as a double page spread. On the left-hand side was the claim in question 'as patients age, their response to [standard vaccines] may decline. Target your over 75s with Inflexal V' while on the right-hand side was a bar chart depicting the results of Conne *et al*. The bar chart was headed 'Proportion of elderly patients seroprotected against the three flu strains contained in the vaccines'. The results shown were 68% for Inflexal V and 38% for a subunit vaccine (p=0.01). A footnote to the bar chart stated that the mean age of the 72 patients was 80 years. Given the claim on the left-hand page and the footnote to the bar chart the Panel considered that many readers would assume that the studies referenced in the leavepiece related only to patients aged over 75 which was not so. The Panel considered that the leavepiece was misleading in that regard. Breaches of Clauses 7.2 and 7.4 were ruled.

Complaint received **13 April 2004**

Case completed **8 June 2004**

GENERAL PRACTITIONER v GLAXOSMITHKLINE

Seretide journal advertisement

A general practitioner complained about a journal advertisement for Seretide (salmeterol/fluticasone) issued by GlaxoSmithKline which featured a photograph of a couple walking, one behind the other, along a dry stone wall in a countryside setting. The headline read 'Have you ever heard someone's heart sing?'.

The complainant did not consider that the picture was appropriate; showing adults walking on top of a dry stone wall encouraged inappropriate use of the wall. Walking on top would cause the wall to collapse and stock to escape. It would not make the farmer happy!

The Panel considered that the photograph of a couple walking along a dry stone wall beneath the headline 'Have you ever heard someone's heart sing?' was a light-hearted depiction of a couple enjoying themselves. The Panel noted the complainant's view that the photograph encouraged inappropriate use of a dry stone wall. The Panel did not consider that such a view would be shared by a majority of the audience. High standards had been maintained. The Panel thus ruled no breach of the Code.

A general practitioner complained about a journal advertisement (ref SFL/FPA/03/09129/1) for Seretide (salmeterol/fluticasone) issued by GlaxoSmithKline UK Limited. The advertisement featured a photograph of a couple walking, one behind the other, along a dry stone wall in a countryside setting. The headline read 'Have you ever heard someone's heart sing?'.

COMPLAINT

The complainant did not consider that the picture was appropriate; showing adults walking on top of a dry stone wall encouraged inappropriate use of the wall. Walking on top would cause the wall to collapse and stock to escape. It would not make the farmer happy!

When writing to GlaxoSmithKline the Authority asked it to respond in relation to the requirements of Clauses 9.1 and 9.2.

RESPONSE

GlaxoSmithKline stated that it understood the environmental concern on this matter but did not consider it constituted a breach of the Code.

The process of developing the image for this advertisement was thorough, intending to convey a sense of release from the restrictions of asthma. Asthma could have a significant impact on patients' lives, causing self-imposed restrictions of activities due to their symptoms. A number of health professional advisory panels were consulted to support the development of this campaign. Since the advertisement was only being used with health professionals and not the general public, GlaxoSmithKline considered the photograph was acceptable and would not encourage inappropriate use of the wall.

GlaxoSmithKline stated that it had carefully considered the environmental issues that had been raised and that it had considered the issue of walking on dry stone walls. In addition, the photograph was taken on private land, with the consent of the landowner, and great care and attention was taken to ensure that no damage was caused to the wall. This image was not used in any non-promotional way with the general public and as such the only people who would view it were health professionals.

GlaxoSmithKline submitted that the image itself and the thorough and responsible way it was chosen and developed, demonstrated that it had maintained high standards. The company had also recognised the professional nature of the audience, who it would not expect to be influenced to walk upon dry stone walls by this advertisement.

PANEL RULING

The Panel considered that the photograph of a couple walking along a dry stone wall beneath the headline 'Have you ever heard someone's heart sing?' was a light-hearted depiction of a couple enjoying themselves. The Panel noted the complainant's view that the photograph encouraged inappropriate use of a dry stone wall. The Panel did not consider that such a view would be shared by a majority of the audience. High standards had been maintained. The Panel thus ruled no breach of Clauses 9.1 and 9.2 of the Code.

Complaint received **13 April 2004**

Case completed **19 May 2004**

CASE AUTH/1578/4/04

PFIZER v LILLY

Cialis folder

Pfizer complained about a folder entitled 'Patient Preference Studies' which had been issued by Lilly in its promotion of Cialis (tadalafil) for the treatment of erectile dysfunction (ED). The first page of the folder described Govier *et al* (2003) which evaluated patient preference for Cialis 20mg vs Pfizer's product Viagra (sildenafil) 50mg during treatment initiation for ED. The second page described Ströberg *et al* (2003) in which current Viagra users were switched to Cialis 20mg and then asked which treatment they preferred. The third page was headed 'Conclusions' and included the claims at issue below. The fourth page included a pocket in which were placed reprints of the two studies.

Pfizer noted that in Govier *et al* patients were treated for a month with either Viagra 50mg or Cialis 20mg. After a 1 week wash-out period, they then received the other medicine for another month. 66.3% of patients stated a preference for Cialis and 33.7% preferred Viagra.

Pfizer alleged that the claim 'Patients preferred Cialis 20mg over sildenafil 50mg' was misleading. There was no mention that the maximum dose of Cialis had been compared with the starting dose of Viagra. These data were therefore meaningless to establish true patient preference. Pfizer further noted that the instructions provided with Cialis included the favourable statement that on using the treatment men might find their sex lives 'more flexible and less planned'.

Pfizer noted that the authors acknowledged that the limitations of the study included its short duration, the differing dosages used, the possibility that the result might be different if other dosages were used and the differing dosage instructions. The authors concluded that additional studies using higher dosage of Viagra with longer treatment periods would help to understand treatment preferences. Pfizer alleged that in view of these limitations the claim was in breach of the Code.

The Panel considered that the claim 'Patients preferred Cialis 20mg over sildenafil 50mg' was not a fair reflection of the data. No mention was made that the data related to initiation of treatment for ED over a four week period and the authors' view that the results would not necessarily translate to long-term preferences. The comparison was between the recommended dose of Viagra and the maximum dose of Cialis. The Panel noted that the Viagra summary of product characteristics (SPC) gave a recommended dose of 50mg and based on efficacy and toleration the dose could be increased to 100mg or decreased to 25mg. The Cialis SPC stated that 20mg could be tried in patients for whom 10mg did not produce an adequate effect. The study authors noted that the difference in preference may have been less (or more) pronounced had Cialis 10mg or Viagra 100mg been used. Studies using higher doses of Viagra and longer treatment periods would add to the understanding of the treatment preferences of patients with ED. Most patients had never taken Viagra and none had ever taken Cialis. None of these limitations were explained in the description of the study on page 2 of the folder.

The Panel also noted the authors' statement that the dosing instructions might have introduced an additional source of bias. It also noted that the study was designed to ensure that differences in dosing instructions would not compromise the blinding of patients or investigators. The Panel considered that the claim was an unfair comparison. The results had not been presented within the context of the overall limitations of the study. The Panel ruled breaches of the Code.

Pfizer noted the claim '90% of men who had previously used sildenafil 25-100mg chose to use Cialis [20mg] in the study extension for the treatment of their ED'. The company stated that in Ströberg *et al* patients who had taken a fixed dose of Viagra (25-100mg) for 6-24 weeks underwent 3 weeks of assessment on Viagra (25-100mg) and a 1 week wash-out phase. Patients were then given Cialis 20mg for 6 weeks, followed by a 3 week assessment phase. Having had both treatments patients were asked which they would prefer for a 6 month extension phase and of 147 patients 90% expressed a preference for Cialis while 10% preferred Viagra. Pfizer noted, however, that it was accepted that in preference studies patients preferred the most recently taken treatment. At the time of assessing patient preference all had taken Cialis for 9 weeks. A crossover study would eliminate this potential bias.

Whilst Pfizer acknowledged that the instructions differed for the two products, care must be taken in studies to ensure that no bias was introduced. The Cialis dosing instructions went beyond the basics and stated that patients might find their 'sex life more flexible and spontaneous' if they took study medication well in advance of any anticipated sexual activity. This positive message about the product would influence patient preference.

The authors stated that limitations of the study design included the 'flexibility and spontaneity' messages that were provided with Cialis, the maximum dosage of Cialis was compared to varying dosages of Viagra (only 35% of patients taking the maximum dosage of Viagra were allowed into the study). The authors stated that randomised, double-blind designs and questionnaires that examined the reasons why patients switched from one therapy to another were needed to answer questions on patient preference that were scientifically rigorous.

Pfizer stated that from the above and given the limitations of the study design, these data and their use in promotional material were in breach of the Code.

The Panel noted that Ströberg *et al* evaluated patients' preferences for Cialis or Viagra by determining the proportion of current sildenafil

users who would, after a period of treatment with Cialis, elect to continue treatment with Viagra or switch to Cialis 20mg for a longer period. Ströberg *et al* concluded that in this short-term, open label study such patients preferred to switch to Cialis by a ratio of approximately 9:1. Ströberg *et al* noted that although the study sought to mimic the experience of actual patients the results were subject to potential limitations due to the design of the study which included, *inter alia*, differences in dosing instructions and dosages for Viagra and Cialis.

The Panel did not accept Lilly's submission that the design problems of the Ströberg *et al*, ie the lack of crossover, were answered by the results of the Govier *et al*. Both the design of Ströberg *et al* and the difference in dosing instructions would introduce bias. The Panel noted that its comments above about the dosing of Cialis were also relevant here and considered that the claim '90% of men who had previously used sildenafil 25-100mg chose to use Cialis [20mg] in the study extension for the treatment of their ED' was an unfair comparison. Breaches of the Code were ruled.

Pfizer alleged that it was inappropriate to have promotional material which focused exclusively on the maximum dosage of Cialis. The promotional material was not in line with the SPC. Further, to make comparisons at this dosage, as was the aim of this material, was potentially misleading. Pfizer alleged a breach of the Code.

The Panel noted that the use of claims based on Govier *et al* and Ströberg *et al* had been ruled in breach of the Code above for, *inter alia*, the dose of Cialis. This aspect of the present allegation had thus already been addressed. The Panel however did not consider that the promotion of Cialis 20mg was inconsistent with its SPC and on this narrow point ruled no breach of the Code.

Pfizer Limited complained about the promotion of Cialis (tadalafil) by Eli Lilly and Company Limited. Cialis and Pfizer's product Viagra (sildenafil) were both licensed to treat erectile dysfunction (ED).

The item at issue was a folder (ref C1585) entitled 'Patient Preference Studies'. The first page described Govier *et al* (2003) which was a double-blind cross over study to evaluate patient preference for Cialis 20mg versus Viagra 50mg during treatment initiation for ED. The second page described Ströberg *et al* (2003) which was an open label study investigating patient preference. ED patients were switched from Viagra to Cialis 20mg. The third page was headed 'Conclusions' and included the claims at issue in points 1 and 2 below.

The fourth page included a pocket in which were placed reprints of the two studies.

1 Claim 'Patients preferred Cialis 20mg over sildenafil 50mg'

COMPLAINT

Pfizer stated that Govier *et al* had enrolled 215 men who were randomised to 4 weeks' treatment with either Viagra 50mg or Cialis 20mg. This was followed by a 1 week wash-out period, followed by crossover and treatment with the other medicine for another 4 weeks. Following this treatment period patients were asked which treatment they preferred by way of a questionnaire. The study concluded that 66.3% of patients preferred Cialis 20mg and 33.7% preferred Viagra 50mg.

Pfizer was concerned about the limitations of the study (as acknowledged by the authors) and the subsequent use of the data in promotional material, which it alleged would mislead health professionals.

Pfizer alleged that the claim suggested that Cialis 20mg was the preferred treatment option over Viagra 50mg. Although the dosages were specified, there was no clear mention to clinicians that the dosages that were compared represented the maximum dosage of Cialis and only the starting dose of Viagra. These data were therefore meaningless to establish true patient preference if the highest dosage of one medicine was used and compared to the lower starting dosage of a comparator. Pfizer alleged that the data should not be used in promotional material as they represented an incorrect comparison of the two treatments and were therefore misleading.

Pfizer referred to the dosing instructions provided to men taking Cialis which stated that on using the treatment 'they may find their sex life is more flexible and less planned'. This statement was in favour of Cialis as assumptions were being made about the product, which attributed positive messages about it. This was likely to result in patients expressing a preference for this treatment.

Pfizer pointed out that the authors acknowledged the limitations of the study in their discussion. This included the short duration of the study, the differing dosages used, the possibility that the result might be different if other dosages were used and acknowledgement of the differing dosage instructions.

The authors concluded that additional studies exploring the higher dosage of Viagra with longer treatment periods would help to understand treatment preferences.

Pfizer alleged that in view of the limitations of the study, as outlined, and in particular the differing dosages and dosing advice, the claim was in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

Lilly stated that the folder summarised two peer-reviewed articles addressing the topic of patient preference between Cialis and Viagra. This folder was produced in November 2003 at which time the enclosed papers were the only peer-reviewed papers published on patient preference. It had been available for use by the specialist sales force only for distribution to health professionals.

With regard to the comparison of the maximum dosage of Cialis and the starting dose of Viagra, Lilly acknowledged that if the data were presented to physicians in isolation they could be misleading. However, as Pfizer acknowledged, the folder itself

made it quite clear which doses of Cialis and Viagra were compared, and presented the data with the original peer-reviewed article which made quite clear the different doses used. Lilly emphasised that Govier *et al* was not presented in isolation, but together with Ströberg *et al* in which Cialis 20mg was compared with Viagra 100mg.

Lilly strongly rejected Pfizer's view that the data were 'meaningless'. However, in recognition of the limitations of the data they were presented alongside similar data obtained from a different study design and with the original peer reviewed articles. The papers were published consecutively in the journal Clinical Therapeutics, so that they would be seen and read together. Lilly submitted that the data were far from meaningless but helped build an overall picture of patient preference.

With regard to Pfizer's view that the dosing instructions provided to patients taking Cialis were likely to result in patients expressing a preference for that treatment Lilly noted that Govier *et al* was a double-blind study. This double-blinding was maintained by a complicated series of alternative arms in which patients might receive placebo with either Viagra or Cialis dosing instructions or even Cialis with Viagra instructions. Govier *et al* stated that '… [these alternate arms] ensured that differences in dosing instructions would not compromise the blinding of patients or investigators'. Thus the design of the study and the paper itself contradicted Pfizer's assertion that the dosing instructions were likely to result in patients expressing a preference.

With regard to Pfizer's comment that that the authors' acknowledgement of the limitations of the study in some way made the results and conclusions misleading, Lilly submitted that it was well understood that the discussion section of all peer-reviewed publications discussed potential limitations of the study concerned. The important principle to establish was that such discussion, as part of a peer reviewed publication, did not invalidate the presentation or use of the data in promotion. Pfizer specifically highlighted the authors' point that additional studies exploring higher doses of Viagra with longer treatment periods would help to understand treatment preference. It was these very comments of the authors that had prompted Lilly to present Govier *et al* with Ströberg *et al* where higher doses of Viagra (100mg) were compared with Cialis for a longer period of time. In Ströberg *et al* there was an 89% preference expressed by patients for Cialis 20mg over Viagra 100mg.

Lilly did not accept that the material was in breach of Clause 7.2 or 7.3 of the Code.

PANEL RULING

The Panel noted that the claim at issue appeared on page 4 of the folder headed 'Conclusions' facing the brief description of Ströberg *et al* on page 3. Brief details of Govier *et al* appeared on page 2.

The Panel considered that the claim 'Patients preferred Cialis 20mg over sildenafil 50mg' was not a fair reflection of the data. For example no mention was made that the patient preference data related to initiation of treatment for ED over a four week period and the authors' view that the results would not necessarily translate to long term preferences. The comparison was between the recommended dose of Viagra and the maximum dose of Cialis. The Panel noted that the Viagra summary of product characteristics (SPC) gave a recommended dose of 50mg and based on efficacy and toleration the dose could be increased to 100mg or decreased to 25mg. The Cialis SPC stated that 20mg could be tried in patients for whom 10mg did not produce an adequate effect. The Panel queried whether the dosing in the study was in line with the SPC. The study authors noted that the difference in preference might have been less (or more) pronounced had Cialis 10mg or Viagra 100mg been used. Additional studies exploring the response to higher doses of Viagra and longer treatment periods would help further investigate and add to an understanding of the treatment preferences of patients with ED. Most of the patients were Viagra naïve and none of them had ever taken Cialis. None of these limitations were explained in the description of the study on page 2 of the folder.

The Panel also noted the authors' statement that the dosing instructions might have introduced an additional source of bias. It also noted that the study was designed to ensure that differences in dosing instructions would not compromise the blinding of patients or investigators.

The Panel considered that the claim was an unfair comparison. The results had not been presented within the context of the overall limitations of the study. The Panel ruled breaches of Clauses 7.2 and 7.3 of the Code.

2 Claim '90% of men who had previously used sildenafil 25-100mg chose to use Cialis [20mg] in the study extension for the treatment of their ED'

COMPLAINT

Pfizer stated that Ströberg involved patients who had taken Viagra for at least 6 weeks (maximum 24 weeks) on a fixed dose (25-100mg), and were then put through 3 weeks of assessment on Viagra (25-100mg) and a 1 week wash-out phase. Following which they were given Cialis 20mg for 6 weeks, followed by a 3 week assessment phase. Patients were then asked which treatment they would prefer for a 6 month extension phase. Of the 147 patients who completed the preference question, 90% expressed a preference for Cialis 20mg, while 10% expressed a preference for Viagra (25-100mg).

Pfizer was concerned about the limitations of this study to make meaningful conclusions for use in promotional material.

Pfizer pointed out that an accepted occurrence in preference studies was patients preferring the most recently taken treatment. At the time of assessing patient preference all patients would have been taking Cialis for a total of 9 weeks. A crossover study would

eliminate the potential bias that might occur in this type of study.

The instructions given to each treatment group also differed significantly. Whilst Pfizer acknowledged that the instructions differed for the two products, care must be taken in studies to ensure that no bias was introduced. The dosing instructions with Cialis went beyond basic dosing instructions and included the instructions that patients might find their 'sex life more flexible and spontaneous' if they took study medication well in advance of any anticipated sexual activity. This attributed positive messages about the product which would influence patient preference.

The authors in their discussion stated the limitations of the study design. These included the 'flexibility and spontaneity' messages that were provided with Cialis dosing. That the study compared the maximum dosage of Cialis to varying dosages of Viagra (only 35% of patients taking the maximum dosage of Viagra were allowed into the study).

The authors also stated that randomised, double-blind designs and questionnaires that looked into the reasons why patients switched from one therapy to another were needed to really answer questions on patient preference that were scientifically rigorous.

Pfizer alleged that from the above and considering the limitations of the study design, these data and their use in promotional material were in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

With regards to Pfizer's view that, 'a crossover study would eliminate the potential bias…,' Lilly submitted that this again highlighted the importance of presenting these two sets of data together. Govier *et al* clearly demonstrated that, certainly in the case of Viagra and Cialis, treatment preference was not influenced by treatment sequence. Indeed the treatment preference for Cialis was numerically greater when Cialis treatment preceded Viagra.

Lilly agreed with Pfizer that a crossover design, in principle, eliminated the potential for bias but Govier *et al* demonstrated that such a bias did not exist.

Lilly did not accept Pfizer's view that the dosing instructions used for Cialis would influence patient preference. This again highlighted the importance of presenting these data together. Govier *et al* with its double-blind design showed a preference for Cialis with any potential bias from the dosing instructions removed. In Ströberg *et al* the subjects entering the study were experienced Viagra users with a mean of 15 weeks' Viagra use. Pfizer and the authors acknowledged that the way in which Cialis was utilised was very different from Viagra. Thus, to minimise any potential bias that comparing 15 weeks' use of Viagra with 9 weeks' use of Cialis might impart, the dosing instructions for Cialis were more detailed.

With regard to Pfizer's points about the limitation of Ströberg *et al* noted by the authors, Lilly referred to its response at point 1 above. In addition, Lilly agreed with Pfizer that Ströberg *et al* compared various doses of Viagra with Cialis. Ströberg *et al* demonstrated an overall preference of 90% for Cialis, but more importantly, a preference of 89% for Cialis 20mg over the maximum dose, 100mg, of Viagra and thus answering the request of Govier *et al* for additional studies exploring patient preference with higher doses of Viagra. Lilly submitted that this had completely validated its position and it did not therefore accept that it was in breach of Clauses 7.2 or 7.3 of the Code.

In response to Pfizer's statement that only 35% of patients taking the maximum dose of Viagra were allowed into the study, Lilly noted that the authors had stated that this was to ensure that the study population adequately represented patients seen in Europe. This percentage of patients still enabled a statistically significant 89% preference for Cialis 20mg over Viagra 100mg to be demonstrated ($p<0.01$).

Lilly did not accept that the material was in breach of Clauses 7.2 or 7.3 of the Code.

PANEL RULING

The Panel noted that Ströberg *et al* sought to evaluate patients' preferences for Cialis or Viagra in a cohort of current Viagra users by determining the proportion of men who would, after a period of treatment with Cialis, elect to continue treatment with Viagra or switch to Cialis 20mg for a longer period. Ströberg *et al* concluded that in this short-term, open label study such patients preferred to switch to Cialis by a ratio of approximately 9:1. Ströberg *et al* noted that although the study sought to mimic the experience of actual patients the results were subject to potential limitations due to the design of the study which included, *inter alia*, differences in dosing instructions and dosages for Viagra and Cialis.

The Panel did not accept Lilly's submission that problems with the design of the Ströberg *et al* study, ie the lack of crossover, were answered by the results of the Govier *et al*. Both the design of Ströberg *et al* and the difference in dosing instructions would introduce bias. The Panel noted its comments at point 1 above about the dosing of Cialis which were also relevant here.

The Panel considered that the claim '90% of men who had previously used sildenafil 25-100mg chose to use Cialis [20mg] in the study extension for the treatment of their ED' was an unfair comparison and ruled breaches of Clauses 7.2 and 7.3 of the Code.

3 Promotion of Cialis 20mg

COMPLAINT

Pfizer noted that the recommended starting dosage of Cialis was 10mg. Pfizer alleged that it was inappropriate to have promotional material which focused exclusively on the maximum dosage. The promotional material was not in line with the SPC which recommended that this dosage should only be used if the 10mg dosage did not produce an adequate effect. Clinicians needed to be made aware of the correct starting dosage and to have promotional material exclusively concentrating on the maximum titrated dosage without a clear statement that this was

the case, was incorrect. Further, to make comparisons at this dosage, as was the aim of this material, was potentially misleading. Pfizer alleged a breach of Clause 3.2 of the Code.

Pfizer was very concerned at the use of these data in promotional material. As outlined, the study designs had limitations, which were acknowledged by the authors and Pfizer questioned the scientific rigour. Therefore, Pfizer alleged that the use of these studies in promotional material must be done in a manner that did not mislead as to the overall meaning of these studies.

RESPONSE

Lilly submitted that the folder in question was designed to present both Govier *et al* and Ströberg *et al*. These studies focused on Cialis 20mg and accordingly this dosage formed the focus of the piece. Lilly submitted that the use of Cialis 20mg was within its SPC and accordingly it did not accept that it was in breach of Clause 3.2.

Lilly noted that Pfizer, in its conclusion, questioned the scientific rigour of the studies and that their use in promotional material was misleading. Lilly reminded that these papers were published in a peer-reviewed journal and that the folder presented the data from both these studies in association with reprints of the original papers. Lilly submitted that by presenting these data in this way it maintained that it did not mislead and did not breach Clause 7.2 or 7.3 of the Code.

PANEL RULING

The Panel noted that the issue to be considered was whether promoting Cialis 20mg was in accordance with the marketing authorisation and not inconsistent with the SPC. The Cialis SPC provided that a 20mg dose could be tried in those patients for whom the 10mg dose did not produce an adequate effect.

The Panel noted that the use of claims based on Govier *et al* and Ströberg *et al* had been ruled in breach of the Code at points 1 and 2 above. The dosage of Cialis was one of the reasons why the Panel had ruled breaches of the Code. This aspect of the present allegation had thus already been addressed.

The Panel however did not consider that the promotion of Cialis 20mg was inconsistent with its SPC and on this narrow point ruled no breach of Clause 3.2 of the Code.

Complaint received **15 April 2004**

Case completed **21 June 2004**

CASE AUTH/1581/4/04

SCHWARZ PHARMA v STIEFEL

Promotion of Duac

Schwarz Pharma complained about a detail aid and associated mouse mat used in the promotion of Duac (clindamycin/benzoyl peroxide topical gel) for the treatment of acne by Stiefel. With regard to the detail aid, Schwarz alleged that the use of the quotation from Lookingbill *et al* (1997) 'Our efficacy results with once daily usage [of Duac Once Daily Gel] are quite similar to those shown with twice daily use of a combination erythromycin/benzoyl peroxide preparation' was misleading and could not be substantiated. The erythromycin/benzoyl peroxide preparation could only be Schwarz's own product Benzamycin. Lookingbill *et al* had compared Duac with each of its active ingredients, or with its vehicle, used alone; no comparison had been made with Benzamycin. It appeared that the authors had referred to Shalita *et al* 1992 and Chalker *et al* 1983, neither of which compared Duac with Benzamycin, and had made an anecdotal comparison of the studies without the scientific controls needed to make a comparative claim.

The Panel considered that readers would understand that the quotation related to the results of a direct comparison of Duac with Benzamycin and this was not so. The quotation might be the authors' opinion but nonetheless as it was used in promotional material it had to comply with the Code. There was no direct evidence to support it. The Panel considered that the claim was misleading and not capable of substantiation and breaches of the Code were ruled.

Schwarz noted that the mouse mat described Duac as 'New'. This was a claim for the product and so the mouse mat was inconsistent with the requirements for a promotional aid; prescribing information was needed.

The Panel noted that to be exempt from the need to include prescribing information on a promotional aid it must include no more about the medicine than its name, an indication that the name of the medicine was a trade mark and the name of the company marketing the medicine. 'New' was information about Duac beyond that permitted and the Panel considered that prescribing information was thus required. A breach of the Code was ruled.

Schwarz Pharma Limited complained about the promotion of Duac (a topical gel containing clindamycin 1% and benzoyl peroxide 5%) by Stiefel Laboratories (UK) Limited. Duac was indicated for the treatment of mild to moderate acne vulgaris.

The material at issue was a detail aid (ref D:E3056UK) which included a sleeve containing a mouse mat (ref D:E3129UK).

1 Claim 'Our efficacy results with once daily usage [of Duac Once Daily Gel] are quite similar to those shown with twice daily use of a combination erythromycin/benzoyl peroxide preparation'

Page 8 of the detail aid headed 'Patients are more likely to persist with a treatment they like' included the above quotation from Lookingbill *et al* (1997).

COMPLAINT

Schwarz alleged that the use of the quotation as a comparative claim was misleading, could not be substantiated and was in breach of Clauses 7.2, 7.3 and 7.4 of the Code.

Schwarz stated that 'a combination erythromycin/benzoyl peroxide preparation' could only be its product – Benzamycin (erythromycin 3%, benzoyl peroxide 5%). Lookingbill *et al* compared Duac with clindamycin or benzoyl peroxide or gel vehicle alone; no comparison was made with Benzamycin. It appeared that the authors had referred to two clinical papers (Shalita *et al*, 1992; Chalker *et al*, 1983), which did not compare a combination erythromycin/benzoyl peroxide gel to a clindamycin/benzoyl peroxide combination.

This appeared to be an anecdotal comparison of independent studies without the scientific controls necessary to make such comparative claims.

Schwarz stated that the method of comparison was not scientifically valid and noted that in Lookingbill *et al*, Duac achieved a 35% reduction in inflammatory lesion counts at week 4. By comparison, in Chalker *et al*, Benzamycin achieved a 55% reduction. At the end of the study, Duac showed a 60% reduction compared to Benzamycin's achievement of a 75% reduction in inflammatory lesion counts.

RESPONSE

Stiefel submitted that the quotation was an accurate quotation from Lookingbill *et al*. The authors were recognised worldwide authorities in the treatment of acne; the peer reviewed paper was published in the Journal of the American Academy of Dermatology, a respected journal of high international standing. Stiefel did not accept that it was misleading to use this quotation in its promotional literature since it was a fair and balanced declaration by the authors of their clinical experience. The statement was substantiated by the experience and reputations of the authors concerned and endorsed by peer review in a respected journal.

PANEL RULING

The Panel considered that readers would understand the quotation at issue as relating to the results of a direct comparison of Duac with a erythromycin/benzoyl peroxide preparation and this was not so. Lookingbill *et al* did not directly compare the two products. The quotation might be the authors' opinion but nonetheless as it was used in promotional material it had to comply with the Code. There was no direct evidence to support it.

The Panel considered that the claim was misleading and not capable of substantiation and ruled breaches of Clauses 7.2, 7.3 and 7.4 of the Code.

2 Mouse Mat

The mouse mat was designed to look like a record with the words 'New' and 'Duac Once Daily Gel' followed by the non-proprietary name. The mouse mat also included the company name.

COMPLAINT

Schwarz alleged that the mouse mat included more than the information permitted by Clause 18.3.

Use of the word 'New' on the left side of the record label constituted a claim and thus prescribing information was required. The mouse mat was not consistent with the requirements for a promotional aid. A breach of Clause 4.1 was alleged.

RESPONSE

Stiefel stated that the mouse mat formed a part of the detail aid used by its representatives when explaining the product to prospective prescribers. Once the representatives had completed their description of the product, the mouse mat was given to the prescriber as a memory aid together with a leavepiece (D: E3068UK) which contained prescribing information as required by the Code. Stiefel submitted that this provided the prescriber with more easily referenced access to the prescribing information than would be the case if it had been printed on the mouse mat. The mouse mat declared that Duac was a new product which was a fact.

PANEL RULING

The Panel noted that to be exempt from the need to include prescribing information on a promotional aid it must include no more about the medicine than its name, an indication that the name of the medicine was a trade mark and the name of the company marketing the medicine.

The mouse mat included the word 'New' which was information about the medicine beyond that permitted by Clause 18.3 of the Code. The Panel considered that the mouse mat did not meet the requirements of Clause 18.3 and thus prescribing information was required. The Panel thus ruled a breach of Clause 4.1 of the Code.

Complaint received **26 April 2004**

Case completed **14 June 2004**

CASE AUTH/1584/4/04

PIERRE FABRE v AVENTIS PHARMA

Taxotere booklet

Pierre Fabre noted that, in a booklet entitled 'Taxotere Clinical [docetaxel] Overview' and issued by Aventis Pharma, a section headed 'Recommendation from the Scottish Medicines Consortium [SMC] No.42' stated 'The first national evaluation of Taxotere in combination with cisplatin for 1st-line treatment of unresectable, locally advanced or metastatic NSCLC [non small cell lung cancer], recommends Taxotere + cisplatin as an effective treatment option. The recommendation goes on to highlight the unique advantages for the Taxotere combination over vinorelbine + cisplatin with respect to quality of life'. Pierre Fabre supplied Navelbine (vinorelbine).

Pierre Fabre stated that in the 'Recommendation' section of the original document from the SMC there was no advice to use the Taxotere combination on the basis of any quality of life advantage. The 'Summary of evidence on comparative efficacy' section of the document reported the results of the TAX 326 study and stated 'there were no significant differences between docetaxel + cisplatin and vinorelbine + cisplatin in change from baseline to end of treatment LCSS [Lung Cancer Symptom Scale] global score, the primary quality of life measure, or KPS [Karnofsky performance status]'. The text then described other individual and lesser quality of life measures where some benefit was seen for the Taxotere arm.

It was clear that this supporting evidence was not part of the recommendation from the SMC, and did not substantiate the superiority claim made. The quality of life findings could not be described as unique advantages for Taxotere. Pierre Fabre alleged that the description of the SMC No.42 recommendation was exaggerated and all-embracing.

The Panel noted that SMC Recommendation at issue read:

'Docetaxel, in combination with cisplatin, is an effective treatment option for the first-line treatment of unresectable, locally advanced or metastatic (stage III/IV) non-small cell lung cancer (NSCLC). In common with the other drugs recommended by Quality Improvement Scotland (QIS) for this condition, benefit has only been proven in patients with good performance status. The estimated cost per quality adjusted life year (QALY) gained is relatively high. Docetaxel should be initiated by respiratory physicians/ oncologists experienced in the treatment of NSCLC'.

The SMC recommendation was reflected in the first sentence of the section in the booklet at issue ie 'The first national evaluation of Taxotere in combination with cisplatin for the 1st-line treatment of unresectable, locally advanced or metastatic NSCLC recommends Taxotere + cisplatin as an effective treatment option'. The following sentence of the section at issue ie 'The recommendation goes on to highlight the unique advantages for the Taxotere combination + cisplatin with respect to quality of life' did not appear as part the recommendation as recorded in the SMC document.

The Panel considered that there was evidence to support quality of life advantages for Taxotere plus cisplatin over vinorelbine plus cisplatin in the SMC summary of evidence on comparative efficacy. These advantages were not mentioned in the SMC Recommendation. The impression given in the booklet was that the recommendation highlighted the advantages of the Taxotere combination over vinorelbine plus cisplatin with respect to quality of life and considered these advantages to be unique; this was not so. The Panel considered that the section in the booklet at issue was thus misleading and exaggerated the SMC recommendation. A breach of the Code was ruled.

Pierre Fabre Ltd complained about the promotion of Taxotere (docetaxel) by Aventis Pharma Ltd.

The material at issue was a 24 page booklet entitled 'Taxotere Clinical Overview' (ref TAX 9661003). A section on page 18 headed 'Recommendation from the Scottish Medicines Consortium [SMC] No.42' stated 'The first national evaluation of Taxotere in combination with cisplatin for 1st-line treatment of unresectable, locally advanced or metastatic NSCLC [non small cell lung cancer], recommends Taxotere + cisplatin as an effective treatment option. The recommendation goes on to highlight the unique advantages for the Taxotere combination over vinorelbine + cisplatin with respect to quality of life'.

Pierre Fabre supplied Navelbine (vinorelbine).

COMPLAINT

Pierre Fabre noted that in the 'Recommendation' section of the original document from the SMC there was no advice to use the Taxotere combination on the basis of any quality of life advantage. The 'Summary of evidence on comparative efficacy' section of the document reported the results of the TAX 326 study and stated 'there were no significant differences between docetaxel + cisplatin and vinorelbine + cisplatin in change from baseline to end of treatment LCSS [Lung Cancer Symptom Scale] global score, the primary quality of life measure, or KPS [Karnofsky performance status]'. The text then described other individual and lesser quality of life measures where some benefit was seen for the Taxotere arm.

It was clear that this supporting evidence was not part of the recommendation from the SMC, and also did not substantiate the superiority claim made in the booklet. In addition the quality of life findings could not be described as unique advantages for Taxotere.

Pierre Fabre alleged that the description of the SMC No.42 recommendation was in breach of Clause 7.10 of the Code in that it was exaggerated and all-embracing; use of the word 'unique' implied a general superiority which was not so.

RESPONSE

Aventis stated that the section referring to the recommendation from the SMC on the use of Taxotere

plus cisplatin for the treatment of advanced NSCLC was based upon a detailed review of the data.

The booklet referred to the full recommendation from the SMC to substantiate all claims relating to the recommendation. Upon request from Pierre-Fabre, Aventis provided the full recommendation that encompassed a single page summary and the full review document. The SMC recommendation and the information upon which this was based were not separate. Clearly the review of the evidence provided the rationale for the final recommendation.

Aventis was aware of the implications of the use of the word 'unique' and considered that in light of the evidence for Taxotere plus cisplatin, with respect to quality of life, and as described by the SMC, the use of this word was appropriate.

In its review of the evidence for Taxotere plus cisplatin, the SMC critically reviewed the quality of life analysis from the TAX 326 study. It stated that in some areas there was no quality of life difference between Taxotere + cisplatin and vinorelbine + cisplatin, but in others there were differences that favoured the Taxotere + cisplatin arm.

Aventis submitted that it had been careful not to specify or suggest a quality of life advantage where there was no evidence to support this. However, the study showed that validated quality of life measures showed a significant difference in favour of Taxotere + cisplatin. It was critical to note that there were no quality of life advantages favouring the vinorelbine + cisplatin treatment arm. None of the numerous quality of life measures reported a benefit for vinorelbine + cisplatin, greater than Taxotere + cisplatin.

With regard to the use of the word 'unique' Aventis stated that when a benefit was seen in only one direction then that could be termed unique. If there were any quality of life measures where the combination of vinorelbine + cisplatin had been shown to be superior to Taxotere + cisplatin, then clearly the use of the term 'unique' would be unfounded. However, as the data showed and as recognised by the SMC, improvements in quality of life benefits were only evident for Taxotere + cisplatin.

Aventis submitted that it had exerted correct caution in its use of the word 'unique'. To ensure that it was not seen as exaggerated or all-embracing it was clearly specified that this benefit only related to quality of life.

Pierre-Fabre stated that the measures where a significant difference was seen for Taxotere + cisplatin were 'lesser' quality of life measures. Aventis submitted that the key measure where Taxotere + cisplatin reported a significant improvement in quality of life was the EQ-5D. This was an internationally renowned and respected measure of quality of life as it considered 5 specific domains ie mobility, self care, usual activities, pain, and anxiety/depression. These were all factors that significantly impacted on patients and to evaluate the response to this measure of quality of life was a vital part of the TAX 326 study.

Aventis did not accept that the item was in breach of Clause 7.10.

PANEL RULING

The Panel noted that SMC Recommendation at issue read:

'Docetaxel, in combination with cisplatin, is an effective treatment option for the first-line treatment of unresectable, locally advanced or metastatic (stage III/IV) non-small cell lung cancer (NSCLC). In common with the other drugs recommended by Quality Improvement Scotland (QIS) for this condition, benefit has only been proven in patients with good performance status. The estimated cost per quality adjusted life year (QALY) gained is relatively high. Docetaxel should be initiated by respiratory physicians/oncologists experienced in the treatment of NSCLC'.

The SMC recommendation was reflected in the first sentence of the section in the booklet at issue ie 'The first national evaluation of Taxotere in combination with cisplatin for the 1st-line treatment of unresectable, locally advanced or metastatic NSCLC recommends Taxotere + cisplatin as an effective treatment option'. The following sentence of the section at issue ie 'The recommendation goes on to highlight the unique advantages for the Taxotere combination + cisplatin with respect to quality of life' did not appear as part the recommendation as recorded in the SMC document.

Two pages of the summary of evidence on comparative efficacy had been provided. From the two pages provided the status of the evidence or who had produced it were not clear to the Panel. With regard to quality of life outcomes the document stated:

'In the main trial quality of life (QoL) was assessed via Lung Cancer Symptom Scale (LCSS), EuroQoL-5D (EQ-5D) and Karnofsky performance status (KPS). There were no significant differences between docetaxel plus cisplatin and vinorelbine plus cisplatin in change from baseline to end of treatment LCSS global score, the primary QoL measure, or KPS. However, EQ-5D score deteriorated significantly less in the docetaxel plus cisplatin group over this period. During treatment significantly fewer patients in this group experienced weight loss ≥ 10%. The LCSS pain score was also significantly improved in the docetaxel plus cisplatin group from baseline to end of treatment. However, the percentage of patients requiring opioids at baseline and during treatment were the same in all groups'.

The following paragraph in the summary of evidence on comparative efficacy was headed 'Comparative Efficacy'. It discussed the National Institute of Clinical Excellence (NICE) technology appraisal of paclitaxel, gemcitabine and vinorelbine in the first line treatment of NSCLC which included a few trials assessing these medicines in combination with cisplatin. All were associated with similar median survival times and estimated survival times. These were comparable to the survival outcomes with docetaxel plus cisplatin. Quality of life data did not indicate a significant advantage for any particular regimen reviewed by NICE. The document further stated that in the main docetaxcel trial some statistically significant differences in quality of life

outcomes were demonstrated for docetaxcel plus cisplatin compared with vinorelbine plus cisplatin. However, these differences were less than 5 points on 100 point scales.

The Panel considered that there was evidence to support quality of life advantages for Taxotere plus cisplatin over vinorelbine plus cisplatin in the SMC summary of evidence on comparative efficacy. These advantages were not mentioned in the SMC Recommendation. The impression given in the booklet was that the recommendation highlighted the advantages of the Taxotere combination over vinorelbine plus cisplatin with respect to quality of life and considered these advantages to be unique; this was not so. The Panel considered that the section in the booklet at issue was thus misleading and exaggerated the SMC recommendation. A breach of Clause 7.10 of the Code was ruled.

Complaint received **28 April 2004**

Case completed **14 June 2004**

CODE OF PRACTICE REVIEW – AUGUST 2004

Cases in which a breach of the Code was ruled are indexed in **bold type**.

1405/1/03	**Norgine v Schwarz Pharma**	**Promotion of Idrolax**	**Breaches Clauses 7.2, 7.4 and 10.1** **Public reprimand by ABPI Board**	**Appeal by complainant** **Report from the Authority to Appeal Board** **Report from Appeal Board to ABPI Board**	**Page 3**
1544/1/04	**Janssen-Cilag v Napp**	**Promotion of OxyContin**	**Breaches Clauses 2 and 3.2** **Two breaches Clause 7.2** **Breaches Clauses 7.10 and 9.1**	**Appeals by complainant and respondent**	**Page 11**
1545/1/04	**Primary Care Trust Head of Prescribing and Pharmacy Services v GlaxoSmithKline**	**Glitazone guidelines**	**Breaches Clauses 2, 9.1, 10.1 and 15.2**	**No appeal** **Report from Appeal Board to ABPI Board**	**Page 24**
1547/1/04	**Procter & Gamble v Ivax**	**Promotion of Mesren**	**Breaches Clauses 7.2 and 7.4**	**Appeal by respondent**	**Page 26**
1549/1/04	**General Practitioner v Wyeth**	**Arrangements for a meeting**	**Breaches Clauses 15.2 and 15.3**	**Appeal by respondent**	**Page 31**
1556/2/04	General Practitioner v Schering Health Care	Promotion of Levonelle-2	No breach	Appeal by complainant	Page 38
1561/3/04	**General Practitioner v Wyeth**	**Promotion of Zoton FasTab**	**Breaches Clauses 9.1 and 18.1**	**No appeal**	**Page 43**
1562/3/04	Primary Care Trust Chief Pharmacist v Trinity	Conduct of representatives	No breach	No appeal	Page 45
1563/3/04	**GlaxoSmithKline Consumer Healthcare v Pfizer Consumer Healthcare**	**Promotion of Nicorette**	**Six breaches Clause 7.2** **Breaches Clauses 7.4 and 7.8**	**No appeal**	**Page 50**
1565/3/04	NHS Trust Chief Executive and Consultant Physician v Abbott Laboratories	Supply of Humira	No breach	No appeal	Page 60
1566/3/04	Janssen-Cilag/Director v Napp	Alleged breach of undertaking	No breach	No appeal	Page 65
1567/3/04	Lilly v AstraZeneca	Seroquel leavepieces	No breach	No appeal	Page 70
1568/3/04	**General Practitioner v Bayer**	**Market research testing of Avelox edetail**	**Breaches Clauses 4.1, 10.2 and 18.1**	**No appeal**	**Page 77**
1569/3/04	**Hospital Chief Pharmacist v AstraZeneca**	**Nexium IV letter**	**Breaches Clauses 7.2, 7.3 and 7.5**	**No appeal**	**Page 82**

1573/4/04	General Practitioner/ Committee of the Royal College of General Practitioners v Schering Health Care	Yasmin market research	No breach	No appeal	Page 83
1575/4/04	**GlaxoSmithKline v Aventis Pasteur MSD**	**Inflexal V leavepiece**	**Two breaches Clause 7.2 Breach Clause 7.4**	**No appeal**	**Page 85**
1576/4/04	General Practitioner v GlaxoSmithKline	Seretide journal advertisement	No breach	No appeal	Page 88
1578/4/04	**Pfizer v Lilly**	**Cialis folder**	**Two breaches 7.2 Two breaches 7.3**	**No appeal**	**Page 89**
1581/4/04	**Schwarz Pharma v Stiefel**	**Promotion of Duac**	**Breaches Clauses 4.1, 7.2, 7.3 and 7.4**	**No appeal**	**Page 94**
1584/4/04	**Pierre Fabre v Aventis Pharma**	**Taxotere booklet**	**Breach Clause 7.10**	**No appeal**	**Page 96**

PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about sixty non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Nicholas Browne QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).