PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW
NUMBER 42 NOVEMBER 2003

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.

Guidance on appeal procedures

The Authority's Constitution and Procedure provides that rulings of the Code of Practice Panel can be appealed by the parties to the Code of Practice Appeal Board. With the approval of the Appeal Board, the Authority has prepared guidance on the appeal procedures to assist both complainants and respondent companies when lodging an appeal or responding to one. Copies of the guidance will now be included with notifications of Panel rulings and are also available on request to the Authority.

An appeal must be lodged within ten working days of notification of the Panel's ruling and must be accompanied by detailed reasons as to why the ruling is not accepted.

If a company ruled in breach of the Code in relation to a number of allegations appeals some rulings but accepts others, then it must provide, within ten days of notification of the rulings, the requisite undertaking and assurance in respect of those rulings of breaches of the Code which it accepts, ie those which it is not appealing.

Brevity may not always be possible when complex matters are appealed but a clear and concise exposition of the facts should be aimed at. Repetition of the same point should be avoided. All points should be covered in the main text without the use of footnotes. It should be borne in mind, as indicated below, that members of the Appeal Board will have all of the prior documentation before them.

It should also be borne in mind that it must have been possible to substantiate a claim etc on the day it was made.

When a published paper etc is referred to, it should be provided and it assists the Appeal Board if an indication is given as to what members are expected to glean from it and whereabouts in it they should look. There is little merit in merely submitting a large number of published papers without any commentary on them.

Before an appeal is heard each member of the Appeal Board is sent a bound volume (or volumes) which contains the complaint (and its attachments), the response (and its attachments), the Code of Practice Panel minute, the Authority's letters notifying the outcome to the parties, the appeal (and its attachments) and subsequent comments made by the parties (and any attachments). In addition the Appeal Board is provided with copies of the materials at issue and copies of relevant summaries of product characteristics (SPCs).

Where a complaint involved a number of separate issues upon which separate rulings were made there may be a number of rulings appealed, in some cases the complainant and the respondent company appealing different issues. Both the complainant and the respondent company are entitled to appear or be represented before the Appeal Board when an appeal is heard, though they are not obliged to attend and can rely on their written evidence if they prefer. Respondent companies are usually represented. At the hearing the parties are able to make presentations if they wish, and usually do so, though occasionally they just answer questions that members of the Appeal Board may have.

Presentations should be concise, clear and to the point. It should be borne in mind that members of the Appeal Board will already have read the papers in the case. New material, ie material which has not previously been submitted in relation to the case, should not be introduced at the hearing. Presentations should normally last no more than twenty minutes.

Although there is no obligation, the Chairman of the Appeal Board considers it appropriate for each party to have advance sight of any slides which the other party intends to show. In consequence each party will be asked to send legible copies of their slides to the Authority, usually two days prior to the hearing. Once this had been done the slides should not be altered in any way. When the Authority has received both sets of slides it exchanges them between the parties.

When the hearing has been completed, and the parties' representatives have left the room, the Appeal Board determines whether the appeal in relation to each particular ruling has been successful or not. Informal notification of the result is given by telephone to the parties soon after the hearing. Formal written notification follows in due course.

The guidance now available from the Authority gives practical advice upon the issues arising in lodging an appeal or responding to one and should be consulted before preparing the relevant papers.

Use of Clause 2 of the Code

The Code of Practice Appeal Board considered that it would be helpful if information about the use of Clause 2 was published in the Review.

Clause 2 states:

'Activities or materials associated with promotion must never be such as to bring discredit upon, or reduce confidence in, the pharmaceutical industry.'

The supplementary information states:

'A ruling of a breach of this clause is a sign of particular censure and is reserved for such circumstances.'

Although it is difficult to be definitive as there are often many factors that contribute to a ruling of a breach of Clause 2, the following are examples of activities which have previously given rise to a ruling of a breach of Clause 2:

1 In the very rare cases involving material that was potentially harmful to patient safety; for example implying that patients with contraindicated conditions could be prescribed the medicine.

2 In relation to hospitality / meetings where the hospitality was out of proportion to the occasion and / or the educational content was slim.

3 Financial arrangements which amounted to paying doctors to use a medicine.

4 Where there had been a breach of undertaking due to inadequate action by the company.

5 Promotion prior to the grant of a marketing authorization.

6 Where the conduct of employees fell short of reasonably competent care such that their activities might bring discredit upon, or reduce confidence in, the pharmaceutical industry.

7 Multiple / cumulative breaches of a similar nature in the same therapy area by one company within a short period of time.

A ruling of a breach of Clause 2 of the Code does not in itself necessarily mean that sanctions in addition to the usual sanctions, ie withdrawal of material, the signing of an undertaking to avoid similar breaches of the Code in the future and the publication of the case report, are applied. However, given the seriousness of a ruling of a breach of Clause 2 additional sanctions such as an audit are often applied. Occasionally the Appeal Board might report a company to the ABPI Board of Management. The Appeal Board also has the option to require a company to take steps to recover items.

Clause 9.1 states that 'High standards must be maintained at all times' and is often used in circumstances that do not warrant a Clause 2 ruling.

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:

Friday, 16 January

Thursday, 4 March

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

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

How to contact the Authority

Our address is:

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

Telephone: 020 7930 9677
Facsimile: 020 7930 4554

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

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

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

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

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

CASE AUTH/1415/2/03

ROCHE v ORTHO BIOTECH

Promotion of Eprex

Roche complained about the promotion of Eprex (epoetin alfa) by Ortho Biotech in relation to recent safety concerns regarding the anti-erythropoietin antibodies and pure red cell aplasia (PRCA) in patients treated with the product for anaemia associated with chronic renal failure or renal insufficiency. The material in question was a document headed 'What is PRCA?' which appeared on Ortho Biotech's stand at the meeting of the Renal Association in London 2002. Roche supplied NeoRecormon (epoetin beta).

Roche noted that the heading 'What is PRCA?' was supposed to explain what PRCA was but then the document stated that '*suspected* PRCA' (emphasis added) occurred particularly with Eprex. This statement was qualified with 'suspected PRCA has been seen with all major erythropoietic products'. 'Suspected PRCA' was not defined. Roche also noted that a Venn diagram which depicted the relationships between sets of patients introduced the term 'Epoetin-associated PRCA' but did not define it. 'Epoetin-associated PRCA' appeared to represent a small subset of 'Suspected PRCA'. In turn 'Suspected PRCA' was represented as a subset of 'Loss of Clinical Response'. Roche alleged that these terms were ambiguous and ill-defined.

The Panel noted Ortho Biotech's submission that the document was given to health professionals only after they had been taken through a broader document which contained detailed information about the definitions used within the document. In the Panel's view, however, the document in question was a stand alone item.

The document referred to 'suspected PRCA', 'epoetin-associated PRCA', 'antibody-mediated PRCA' and 'loss of clinical response'. The Panel noted that Ortho Biotech had, within the remit of emerging science, discussed these terms with the regulatory authorities and with clinicians. The document included explanations for some of the terms used; 'suspected PRCA', 'BM-confirmed PRCA' and 'Antibody-mediated PRCA'. It appeared that although the terms were being used there was no generally accepted definition for them. The Panel considered that it was misleading not to have defined all the terms used within the document itself. A breach of the Code was ruled in that regard. This ruling was appealed.

Prior to the consideration of the appeal it had come to the Authority's attention that three versions of the material at issue had been supplied. These were similar but not identical. The appeal was considered in relation to the one page version supplied by Roche with its original complaint.

On appeal by Ortho Biotech the Appeal Board noted the company's submission that the document in question would only be provided after the recipient had been taken through a broader document entitled 'Pure Red Cell Aplasia – Background Information' and also a broader discussion as to Ortho Biotech's approach to understanding PRCA. The Appeal Board considered that the document had to be considered as a stand alone item.

The document referred to 'Suspected PRCA', 'Epoetin-associated PRCA', 'antibody-mediated PRCA' and 'Loss of clinical response'. The Appeal Board considered that the highly specialised audience would be familiar with the issues involved in PRCA and hence would have been familiar with the terms used in the document. The Appeal Board did not consider that it was misleading not to have defined all the terms used within the document itself. The Appeal Board ruled no breach of the Code.

Roche noted that the document stated that all erythropoietins carried a risk of immunogenicity. The concept of risk of immunogenicity was unhelpful unless it was put into perspective. Roche alleged that the final statement of the document 'The immune potential of protein medicines can be affected by various factors such as formulation, product storage and handling, route of administration, and other factors' was unhelpful and left the reader wondering what protein medicines, in particular, might be affected by these factors?; did this statement (unreferenced) refer to Eprex, all synthetic erythropoietins or all protein medicines? Roche alleged that Ortho Biotech had misled clinicians into thinking that all protein medicines (including NeoRecormon) had equal problems with antigenicity whereas Roche had no information that this was the case. This generalisation detracted from the specific problem.

The Panel noted that the third bullet point of four beneath the heading of 'What is PRCA' stated 'Recently, physicians began noting rare cases of suspected PRCA in kidney disease patients on erythropoietin products, in particular EPREX'. The following bullet point stated that 'Suspected PRCA has been seen with all major erythropoietic products'. The second and third bullet points, beneath a heading of 'What is antibody-mediated PRCA', read 'Erythropoietin products appear to be less immunogenic than some other protein medicines, but like all administered proteins, they carry a risk of immunogenicity' and 'Antibody-mediated PRCA occurs as a result of an immune response to the protein backbone of recombinant human erythropoietin' respectively. The Venn diagram contained a group labelled 'Epoetin-associated PRCA', there was no subset within that relating only to Eprex-associated PRCA. The Panel considered that although one bullet point referred to the fact that erythropoietin-associated PRCA was noted particularly with Eprex, on balance the document was not sufficiently clear in that regard. There were no details of the incidence of PRCA. The Panel ruled breaches of the Code. These rulings were appealed.

The Appeal Board noted Roche's submission that the summary of product characteristics (SPC) for NeoRecormon stated that 'in very rare cases, neutralising anti-erythropoietin antibodies with or without pure red cell aplasia (PRCA) occurred

during rHuEPO therapy', whereas the Eprex SPC stated that 'Pure red cell aplasia (erythroblastopenia) has rarely been reported in chronic renal failure patients after months to years of treatment with Eprex or other erythropoietins'.

The Appeal Board noted that the Venn diagram contained a group labelled 'Epoetin-associated PRCA', there was no sub-group within that relating only to Eprex-associated PRCA. The Appeal Board considered that although one bullet point referred to the fact that erythropoietin-associated PRCA was noted particularly with Eprex, on balance the document was not sufficiently clear in that regard. Some readers would assume that PRCA was equally associated with all erythropoietin products and this was not so. The Appeal Board upheld the Panel's ruling of breaches of the Code.

Roche noted that it was mentioned only once that suspected PRCA had been noted in 'patients on erythropoietin products, in particular Eprex', but that the document further stated that this undefined suspected PRCA had been seen with all major erythropoietic products. There was no mention that in July 2002, only 6 weeks before this document, Ortho Biotech was asked to send out a 'Dear Doctor' letter explaining that an urgent safety restriction had been placed on Eprex. This resulted in a change to the recommended route of administration of Eprex. Roche considered that, as a stand alone piece, the document omitted major information about Eprex's safety profile. The document did not reflect available evidence and downplayed the role of Eprex antibody-mediated PRCA.

The Panel noted that the document in question was headed 'What is PRCA?'; it was not about Eprex and PRCA *per se*. Some weeks before issuing the document Ortho Biotech had issued a 'Dear Doctor' letter about Eprex and PRCA in which it had given amended advice on route of administration and reminded readers about storage conditions. The Panel did not consider that the purpose of the document now at issue was such that it should also have contained the information given in the 'Dear Doctor' letter. The document was about PRCA generally and not about the safety profile of Eprex in particular. No breach of the Code was ruled in this regard.

Roche noted that the Venn diagram representation of PRCA was not labelled, referenced or referred to in the rest of the document and the terms were not defined. The inference was that epoetin-associated PRCA represented a tiny subset of all suspected PRCA. Ortho Biotech neither referred to nor provided the reader with data to support this claim. Roche had estimated the areas of the circles in the Venn diagram to determine the relative incidences and had concluded that for every 12 cases of suspected PRCA, only one would be epoetin-associated PRCA. The Venn diagram made claims about side effects that did not reflect available evidence and might not be substantiated by clinical experience.

The Panel noted that the Venn diagram depicted three sets: 'Loss of Clinical Response' formed the largest circle; 'Suspected PRCA' was depicted as a small subset within 'Loss of clinical response' and 'Epoetin-associated PRCA' was a small subset within 'Suspected PRCA'. In the Panel's view readers would assume that the relative size of each circle bore some relationship to the relative incidence of each subset shown. Using the area of the circles Roche had calculated the relative incidences of loss of clinical response: suspected PRCA: epoetin-associated PRCA to be 138:12:1. The smallest subset was 'Epoetin-associated PRCA' which, in the Panel's view, in the absence of another subset labelled 'Eprex-associated PRCA', implied that PRCA occurred equally with all epoetins which was not so. The Panel noted that route of administration also affected the incidence of PRCA in Eprex-treated patients; PRCA was more likely to occur if renal patients were given subcutaneous Eprex than if the medicine was administered intravenously. Overall the Panel considered that the Venn diagram was too simplistic; it did not convey the issue of PRCA and epoetin therapy with accuracy. A breach of the Code was ruled. This ruling was appealed.

The Appeal Board noted that at the appeal hearing Ortho Biotech submitted an extract from a detail aid/background document which the company representatives stated had been used by representatives before using the document at issue. The detail aid/background document gave the numbers of the suspected, confirmed and antibody mediated cases of PRCA for Eprex, Procrit/Epogen, NeoRecormon and Aranesp. The number of cases for Eprex were 141 suspected, 114 confirmed and 66 antibody mediated. The totals for all four products were 159 suspected cases, 128 confirmed cases and 71 antibody mediated cases. The Appeal Board noted that Ortho Biotech had confirmed that the terms 'Epoetin associated PRCA' and 'Antibody mediated PRCA' were to be considered synonymous. Overall the Appeal Board considered that the Venn diagram was too simplistic; it did not convey the issue of PRCA and epoetin therapy with accuracy. The Appeal Board upheld the Panel's ruling of a breach of the Code.

Roche noted that the term 'epoetin-associated PRCA' necessarily referred to PRCA secondary to all marketed erythropoietins. Due to the huge imbalance in the number of cases of PRCA seen with Eprex when compared with that seen with other erythropoietins, to refer to 'Epoetin-associated PRCA' as one condition was disingenuous and unfairly denigrated NeoRecormon and was disparaging all epoetins.

The Panel considered that although the diagram gave the misleading impression that PRCA was equally associated with all erythropoietins, it did not downplay the incidence of Eprex-associated PRCA. No breach of the Code was ruled in that regard. The Panel, further, did not consider that the diagram disparaged NeoRecormon or any other epoetin. No breach of the Code was ruled.

With regard to the prescribing information provided on the document Roche alleged that the statement: 'Adults: CRF: Dialysis: IV where feasible' under the

heading 'Dosage and administration', was an over simplification. Section 4.2 of the SPC clearly stated that adult patients on haemodialysis should receive Eprex intravenously. The words 'where feasible' did not refer to haemodialysis patients receiving Eprex.

The Panel noted that under the heading of 'Dosage and administration' the prescribing information stated that adult chronic renal failure patients on dialysis should receive Eprex 'IV [intravenously] where feasible; if not consider risk/benefit of SC route'. The corresponding section of the SPC (dated July 2002) Section 4.2 stated that 'In patients with chronic renal failure the product should be administered by the intravenous route where feasible' and 'In patients on haemodialysis [Eprex] should be administered by the intravenous route'. Readers of the SPC were referred to Section 4.4, Special Warnings and Precautions for use, regarding PRCA where it was stated that Eprex should be administered to chronic renal failure patients by the intravenous route where feasible. The Panel considered that it was inaccurate to state with regard to chronic renal failure patients on dialysis 'IV where feasible' in the prescribing information given the corresponding statement in the SPC. The Panel thus considered that the statement in the prescribing information was not a succinct statement of the information in the SPC with regard to dosage and a breach of the Code was ruled.

Roche Products Limited complained about the promotion of Eprex (epoetin alfa) by Ortho Biotech in relation to safety concerns about Eprex in relation to anti-erythropoietin antibodies and pure red cell aplasia (PRCA). The material in question was a document headed 'What is PRCA?' which appeared on Ortho Biotech's stand at the meeting of the Renal Association in London 2002. Roche supplied NeoRecormon (epoetin beta).

Roche explained that Eprex and NeoRecormon stimulated red blood cell production and were licensed for the treatment of anaemia secondary to chronic renal dysfunction and cancer chemotherapy. Although the active compounds were similar, they were formulated differently.

PRCA was a rare haematological condition in which the bone marrow failed to produce red blood cells. Anti-erythropoetin antibodies as a consequence of epoetin therapy were a newly described cause of this condition. This was a serious safety issue, as the patient must stop epoetin therapy and thereafter might have to be on regular blood transfusions indefinitely. Prior to 1998 epoetins were not associated with PRCA and no reference was made to it in the summaries of product characteristics (SPCs).

In 1999, Casadevall *et al* reported a few cases of anti-erythropoetin antibodies associated with PRCA in renal dialysis patients treated with epoetins to the French Health Authority. In March 2001 the SPC for NeoRecormon was changed to include 'In very rare cases, neutralising anti-erythropoietin antibodies with or without pure red-cell aplasia (PRCA) occurred during rHuEPO therapy' even though this was not a specific epoetin beta effect. No change was made to the Eprex SPC at that time.

In November 2001, Roche understood that Ortho Biotech was directed by the Committee for Proprietary Medicinal Products (CPMP) to change the Eprex SPC and issue a 'Dear Doctor' letter to inform the health profession about the change. According to the letter there were then 40 cases of confirmed or suspected PRCA mostly occurring after 1998.

Data from Casadevall *et al* were published in the New England Journal of Medicine in February 2002 with a follow up letter in April.

In July 2002 the European Pharmacovigilance Working Party of the CPMP, in consideration of a growing number of reports of PRCA associated with Eprex, issued an urgent safety restriction for the product with a resulting change to the SPC advising against its subcutaneous (SC) use in haemodialysis patients, and furthermore that it should only be used under certain circumstances in pre-dialysis. No such restrictions were placed upon NeoRecormon or other epoetins marketed in Europe.

The European Pharmacovigilance Working Party noted at that time:-

'Although a few cases of [PRCA] have also been observed with other marketed erythropoietins (less than about ten cases throughout the world), the great majority of these cases were reported with Eprex.'

In December 2002 notification was circulated from the Medicines Control Agency (MCA) informing prescribers that the SC use of Eprex was now contraindicated in renal patients.

Roche stated that the reason for the increase in PRCA cases was the subject of much debate. However in any review of emerging clinical or scientific opinion certain publications should be cited as highly relevant. Firstly, the original paper and subsequent follow up letter by Casadevall *et al* showed that nearly all reported cases of PRCA were associated with Eprex. Secondly the editorial in the same edition of the New England Journal of Medicine speculated that one of the reasons for the appearance of this problem might have been a change in the manufacture of Eprex in 1998. Communications from one regulatory authority included speculation about a preponderance of cases with SC administration versus IV, and poor adherence to storage instructions on the SPC. Roche noted that Ortho Biotech's parent company had also cited manufacturing and handling issues when presenting the issue to financial analysts in the States, but not to UK health professionals.

COMPLAINT

Roche alleged that the document 'What is PRCA?' provided unhelpful and confusing definitions and graphical representation of PRCA, selective references to published data, unsubstantiated claims about protein medicines and misleading and inaccurate information about the changes to the Eprex SPC.

The heading 'What is PRCA?' was supposed to explain what PRCA was but then the document stated that '*suspected* PRCA' (emphasis added) occurred particularly with Eprex. This statement was qualified with 'suspected PRCA has been seen with all major

erythropoietic products'. 'Suspected PRCA' was not defined. Although suspected PRCA was mentioned throughout the article there was no mention of its converse, confirmed PRCA. Roche also noted that a Venn diagram which depicted the relationships between sets of patients introduced the term 'Epoetin-associated PRCA' but did not define it. 'Epoetin-associated PRCA' appeared to represent a small subset of 'Suspected PRCA'. In turn 'Suspected PRCA' was represented as a subset of 'Loss of Clinical Response' which was also not defined.

The second paragraph was headed 'What is antibody-mediated PRCA?'. This question was answered in the third bullet point. However, it was not clear how the term 'antibody-mediated PRCA' related to suspected, epoetin-associated, confirmed PRCA or indeed loss of clinical response. It was further stated in the document that all erythropoietins carried a risk of immunogenicity. The concept of risk of immunogenicity was unhelpful unless it was put into perspective. The prescriber might wish to know what was the risk of immunogenicity with Eprex; what was the risk compared with other administered proteins and what was the risk compared with other synthetic erythropoietins?

Roche noted that the document contained a quote from Casadevall *et al* (2002): 'Antibodies from all patients bound both glycosylated and deglycosylated ^{125}I-labeled [sic] epoetin with the same efficiency, showing that the antibodies were directed against the protein moiety of the erythropoietin molecule rather than the carbohydrate moiety'. This quotation did not explain why this problem had been predominantly reported with Eprex. Casadevall *et al* reported that out of the 13 patients studied 11 had received Eprex exclusively. In addition 9 more patients with Eprex-associated PRCA were reported in a note added at the proof stage of the published paper. Whilst this remained one of two journal publications to quote case numbers, these figures must now be considered out-of-date themselves and more contemporary numbers would have helped clarify these issues.

The same edition of the New England Journal of Medicine which carried the paper by Casadevall *et al* also published an editorial in which the author speculated that a change in manufacturing of Eprex might be responsible for the recent rise in cases associated with it. There was no reference to this editorial in the document.

Roche considered that the final statement of the document 'The immune potential of protein medicines can be affected by various factors such as formulation, product storage and handling, route of administration, and other factors' was unhelpful and left the reader wondering what protein medicines, in particular, might be affected by these factors?; how might the proteins be affected and what were the consequences of the effect on proteins?; did this statement (unreferenced) refer to Eprex, all synthetic erythropoietins or all protein medicines?; which 'other factors' could affect the immune potential of protein medicines? and which specific factors might have effected the change in immunogenicity of Eprex?

Roche's main objection to the document was that the references to suspected PRCA, epoetin-associated PRCA, antibody-mediated PRCA and loss of clinical response were ambiguous and ill-defined; they did not help the reader decide what the clinical problem was. The definitions and causes of the problem were not based on an up-to-date evaluation of all evidence and did not reflect this evidence clearly, in breach of Clause 7.2. Ortho Biotech had misled clinicians into thinking that all protein medicines (including NeoRecormon) had equal problems with antigenicity whereas Roche had no information that this was the case. This generalisation detracted from the specific problem. In this respect Roche alleged breaches of Clauses 7.2 and 7.4 of the Code.

Roche noted that it was mentioned only once that the reporting of suspected PRCA had been noted by physicians in 'patients on erythropoietin products, in particular Eprex', but that the document further stated that this undefined suspected PRCA had been seen with all major erythropoietic products. The rest of the piece explained how antigenic proteins were as a whole. There was no mention that in July 2002, only 6 weeks before this document, Ortho Biotech was asked to send out a 'Dear Doctor' letter explaining that an urgent safety restriction had been placed on Eprex. This resulted in a change to the recommended route of administration of Eprex. Accordingly Roche considered that, as a stand alone piece, this document omitted major information about Eprex's safety profile; it purported to inform the reader about PRCA, a current and important safety issue, but by omitting the majority of information about it Ortho Biotech had deliberately confused the reader. The document did not reflect available evidence and downplayed the role of Eprex antibody-mediated PRCA. Roche alleged a breach of Clause 7.9.

Roche alleged that the slightly unorthodox Venn diagram representation of PRCA in the top right-hand corner, confused rather than assisted the reader. The diagram was not labelled, referenced or referred to in the rest of the article and the terms were not defined. The inference was that epoetin-associated PRCA represented a tiny subset of all suspected PRCA. Ortho Biotech neither referred to nor provided the reader with data to support this claim. This diagram therefore did not give a clear, fair and balanced view of PRCA, in breach of Clause 7.8 of the Code.

Roche had estimated the areas of the circles in the Venn diagram and determined that the relative incidence of loss of clinical response: suspected PRCA: Epoetin-associated PRCA was about 138:12:1 ie for every 12 cases of suspected PRCA, only one would be epoetin-associated PRCA. This Venn diagram made claims about side effects that did not reflect available evidence and might not be substantiated by clinical experience in breach of Clause 7.9. Once again specific patient numbers were not included.

The term 'epoetin-associated PRCA' necessarily referred to PRCA secondary to all marketed erythropoietins. Due to the huge imbalance in the number of cases of PRCA seen with Eprex when compared with that seen with other erythropoietins, to refer to 'Epoetin-associated PRCA' as one condition was disingenuous and unfairly denigrated NeoRecormon and, although only implicit in this

graph, represented unjustified knocking copy by disparaging all epoetins. Roche alleged a breach of Clause 8.1 of the Code.

Roche noted that in the 'Dosage and administration' section of the prescribing information the following was stated: 'Adults: CRF: Dialysis: IV where feasible'. Roche considered this to be an over simplification. Section 4.2 of the SPC clearly stated that adult patients on haemodialysis should receive Eprex intravenously. The words 'where feasible' did not refer to haemodialysis patients receiving Eprex. Roche interpreted this section of the SPC to mean that in haemodialysis patients where intravenous access was an integral part of their therapy, intravenous administration of Eprex was mandatory. This was inconsistent with the prescribing information on the document in question. Roche alleged a breach of Clause 4.2.

RESPONSE

Ortho Biotech explained that the document 'What is PRCA?' was part of a broader communication to UK nephrologists and the like regarding rare reports of PRCA associated with Eprex. The issue had been extensively discussed amongst this group and had been the subject of two 'Dear Doctor Letters'. The promotional piece was not widely distributed; it was given to customers only after they had been taken through a broader document entitled 'Pure Red Cell Aplasia – Background Information' which contained detailed information about the definitions used within the promotional piece and also broader discussion as to the company's approach to understanding this rare phenomena of PRCA.

Methodology for investigation and reporting of PRCA

Ortho Biotech stated that, in consultation with regulatory authorities worldwide, its parent company had conducted a comprehensive scientific investigation into the increased number of post-marketing reports of loss of (therapeutic) effect where PRCA was suspected in patients treated with Eprex, particularly occurring post 1998.

PRCA was a rare condition characterised by selective failure in the proliferation of red blood cell precursors in the bone marrow resulting in a profound anaemia. PRCA had been associated with auto immune, viral, neoplastic diseases, as well as multiple drug treatments, and more recently with immune-mediated anti-erythropoietin antibodies. The pathophysiology and clinical course of immune-mediated PRCA was not fully understood and was the subject of intense and continued investigation.

In the interest of patient safety, investigations had been far reaching, Ortho Biotech had not eliminated from its communications to health professionals any cases which did not fit a very narrow definition of immune-mediated PRCA. This approach was in keeping with accepted pharmacovigilance practices. Ortho Biotech considered that a broad approach to reporting these events was important given the rarity of cases; spontaneous reporting patterns within different countries; a potentially multi-factorial causation; assay sensitivity of antibody testing not being standardised (particularly between laboratories) and also the emerging scientific and medical understanding as to the true nature of PRCA. Analysis of its data presented to regulatory authorities and health professionals included any report of a patient who had been administered Eprex or any other epoetin therapy, and who had experienced a loss of therapeutic effect which was suspected to be related to PRCA, regardless of availability of bone marrow examination results or evidence of anti-erythropoietin antibodies. Importantly, Ortho Biotech's database did not exclude cases where treatment with multiple epoetin products was reported, ie if any patient had received Eprex at any time, the event was reported as associated with Eprex. Additionally retrospective reviews of in-house safety databases for terms to include PRCA, anaemia, therapeutic response decrease, antibody drug specific, and condition aggravated (anaemia) had ensured completeness of reported cases.

Consequently Ortho Biotech considered that the rigour in which it had investigated and reported to regulatory authorities and health professionals any cases that were suspected to be PRCA (whether proven or not) was done in the most thorough and open way possible. The company therefore strongly refuted all allegations that it had attempted to mislead the medical community in respect of PRCA and its association with Eprex.

Definition of PRCA

Definitive diagnosis of PRCA required a bone marrow biopsy in which there was a reduction exclusively of the erythroid precursor cell line, with other elements being essentially normal. In many patients with chronic disease, such as those with chronic renal failure, such a bone marrow picture might not be so distinct; for example, in myelodysplastic syndromes it was now accepted that PRCA might be a presenting feature of the disease with a mixed morphological picture within the bone marrow. Other factors which made the diagnosis of PRCA, its associative causes and the completion of a database difficult were the rarity of the disease, the difficulty in bone marrow diagnosis and the obtaining and reviewing, in a retrospective manner, bone marrow samples from patients in whom PRCA was suspected. Consequently, and so as not to inadvertently miss any cases, it was decided to construct a database along the following definitions:

Suspected PRCA; these included cases with an apparent loss of therapeutic effect with Eprex treatment and were subsequently reported as having either a bone marrow positive (for PRCA) or bone marrow not performed (or result not known) and where the reporter was suspicious for a possible PRCA.

Bone marrow confirmed PRCA; these were reported cases with severe anaemia characterised by virtual absence of red blood cell precursors in the bone marrow (less than 0.5% erythroblasts) and by a decreased reticulocyte count in blood smear (less than 1%).

Antibody mediated PRCA; these were cases of suspected PRCA (with or without bone marrow confirmation) in which the presence of anti-erythropoietin antibodies had been detected in a patient's serum, regardless of the antibody assay method used.

Ortho Biotech explained that there were two principal types of antibody assays, ELISA and RIA. ELISA was less sensitive but more suited to a broader screening of patients' antibodies, while RIA was more specific, but better suited to small cohorts of patients. As a result of the difficulties of validating the methodology of antibody testing within different laboratories, a central laboratory had been used to investigate the serum samples obtained from patients anywhere in the world, who had been reported to the company as having suspected PRCA. Given that many cases were reported retrospectively, often with very little clinical data, this was not always possible, hence the antibody status of these patients was listed on the database as unknown. Nevertheless, in spite of the inability to confirm absolutely that anti-erythropoietin antibodies existed in such patients, they remained within the database and were reported to the regulatory authorities and the broader medical community as suspected cases of PRCA associated with Eprex.

Response to alleged specific breaches of the Code

Ortho Biotech noted that Roche's main objection to the piece appeared to be that the terms 'suspected PRCA', 'antibody mediated PRCA' and 'loss of clinical response' were all ambiguous and ill-defined. As noted above this was not the case; these terms had been discussed within the remit of emerging science with both the regulatory authorities and also the nephrology community. Ortho Biotech stated that when it discussed its investigations into the phenomena of PRCA with the regulatory authorities, these were the very terms which it had used and had been encouraged to continue to use in order to further understand this relatively new and rare phenomena.

Ortho Biotech noted that Roche also alleged that the definitions and causes of PRCA were not based on an up-to-date evaluation of the evidence in breach of Clause 7.2. At the time of the use of the particular item (November 2002), Ortho Biotech had sent the nephrology community two 'Dear Doctor' letters advising it of the association of PRCA with Eprex and that the majority of cases reported were associated with Eprex (a point the company had consistently stated to the nephrology community and also the regulatory authorities). Further, as the company had undertaken extensive investigations as to the cause of PRCA and also had had ongoing discussions with the regulatory authorities in these matters, it was difficult for it to understand Roche's suggestion that its definitions and hypotheses as to the cause of immune-mediated PRCA were not based on an up-to-date evaluation of all evidence. Additionally, the previous 'Dear Doctor' letters from Ortho Biotech to the nephrology community contained the terms 'suspected PRCA' and 'loss of effect'; these documents were official communications to the medical community, approved through the appropriate regulatory authorities; the inclusion of such terms reflected that they were suitable and reflected the known situation in respect of the pathogenesis of PRCA.

Ortho Biotech strongly refuted Roche's allegation that it had misled clinicians into thinking that all proteins had equal problems with antigenicity. The promotional piece stated that 'Recently, physicians began noting rare cases of suspected PRCA in kidney disease patients on erythropoietin products, in particular, Eprex'. This sentence had not implied an equal preponderance of PRCA between different erythropoietin products; the phrase 'in particular Eprex' strongly suggested that more cases had been reported with Eprex than with other erythropoietins. It was consistent with the message that Ortho Biotech had communicated to the nephrology community and was a point that Ortho Biotech had never denied. The statement made in respect of rare cases of PRCA being noted in renal patients on erythropoietin products was consistent with the facts and consistent with the NeoRecormon SPC. No comparison in respect of incidence between different erythropoietin products had been made and indeed this was the point; the phrase attached to that sentence 'in particular Eprex' emphasised that the problem was greater with Eprex than with other erythropoietins (and here NeoRecormon was not specifically stated). Ortho Biotech thus denied any breach of Clause 7.4.

Roche also appeared to have misunderstood the promotional piece, particularly in respect of the discussion around the cause of antibody formation. The piece clearly indicated that virtually all proteins when introduced into the body could cause an immune response, ie antibody formation. This was consistent with known science. It was then stated that erythropoietin products appeared to be less immunogenic than other protein medicines (biologically active compounds) but like all administered proteins they carried a risk. This again was a known fact; the rather extraordinary feature about the use of erythropoietins in clinical practice was how infrequently immune responses had been noted which was why the recent increased reports of rare cases of antibody-mediated PRCAs principally associated with Eprex, had been the focus of much debate and scientific investigation.

Roche's suggestion that the piece confused readers by omitting information about a current and important safety issue ignored the fact that Ortho Biotech had already sent 'Dear Doctor' letters and other material to the nephrology community explaining the facts surrounding the reports of Eprex-associated PRCA.

Ortho Biotech noted Roche's allegation that this piece had not reflected available evidence and downplayed the role of Eprex antibody-mediated PRCA in breach of Clause 7.9. Ortho Biotech explained that the document could be left with a health professional as long as a more generalised discussion in respect of further background information (including details on the company's investigational approaches and its definitions of PRCA cases and how they were reported) had taken place with the individual. A copy of this background information was provided. Notwithstanding this, within the first bullet point of

the piece at issue, it was stated that 'PRCA is a rare condition'. Clause 7.9 required information and claims about side effects to reflect available evidence or be capable of substantiation. Further it must not be stated that a product had no side effects, toxic effects or risk of addiction, and the word 'safe' must not be used without qualification. Clearly, within this piece, Ortho Biotech had associated Eprex with reports of rare cases of PRCA and the phrase 'in particular Eprex' reinforced the point that the adverse events were more associated with Eprex than other erythropoietins. Stating that the reports were rare did not diminish the importance of PRCA but emphasised that, despite heightened awareness of the condition, it nevertheless remained rare. In this respect, rare was a defined pharmacovigilance term, meaning a reported incidence of approximately 1 in 10,000. This remained the estimated incidence for reports of PRCA associated with Eprex and was consistent with wording used within communications to the nephrology community which were approved by the appropriate regulatory authorities. Ortho Biotech noted that, in particular, it did not use the word 'safe' with or without qualification anywhere in the piece. The company denied a breach of Clause 7.9.

Ortho Biotech noted that Roche had also alleged a breach of Clause 7.8 in respect of artwork and illustrations. Clause 7.8 specified that graphs and tables must be presented in such a way as to give a clear, fair and balanced view of the matter with which they dealt. The Venn diagram to which Roche referred attempted to lead clinicians through more common diagnosis in respect of loss of clinical response to an erythropoietin of which PRCA remained (as defined by pharmacovigilance reporting) a rare event. At the time the piece was used, concern about the incidence of PRCA was greatly heightened, and an attempt was made to educate the nephrology community as to the nature and incidence of PRCA and also how the company might investigate reports of loss of clinical response. Roche had also alleged a breach of Clause 7.9, in that the Venn diagram made claims about side effects which did not reflect available evidence. The incidence of antibody-mediated PRCA was approximately 1 per 100,000 patient years' exposure to IV Eprex and approximately 2 per 10,000 patient years' exposure for the subcutaneous route. This was against the background where Ortho Biotech was receiving numerous reports of 'suspected' PRCA from nephrologists, the majority of which turned out to have other causes for lack of responsiveness to Eprex. This supported the company's assertion that episodes of antibody-mediated PRCA remained rare. Ortho Biotech stated that it had not calculated the actual area of the diagrams as Roche had done as the incidence of antibody-mediated PRCA remained rare, particularly in comparison with the number of reports of suspected PRCA, where other more common causes such as non-compliance, iron deficiency, infection etc were subsequently found for a patient's anaemia; loss of effect was sufficiently common that European Guidelines existed for its management. Despite the fact that it had not calculated areas in the diagram, Ortho Biotech did not consider that the diagram 'played down' the incidence of PRCA associated with Eprex. Ortho Biotech thus denied a breach of Clause 7.9.

Ortho Biotech noted that Roche had also suggested that by using the Venn diagram it had been disingenuous and had unfairly denigrated NeoRecormon, in breach of Clause 8.1. Ortho Biotech noted that this piece made no mention of NeoRecormon, nor did it give any comparison of numbers, since this would be inappropriate, in that no comparative head-to-head studies of NeoRecormon or Eprex had been done in respect of incidence of PRCA. The piece clearly indicated that cases of PRCA were rare, that they might be associated with patients on erythropoietin products and emphasised an association with Eprex. Ortho Biotech therefore denied denigrating erythropoietins and in particular considered that it had not denigrated NeoRecormon directly or indirectly via the contents of this piece. The company denied a breach of Clause 8.1.

Ortho Biotech noted that Roche had also alleged a breach of Clause 4.2 with regard to the Eprex prescribing information. Roche had suggested that in haemodialysis patients intravenous administration of Eprex was mandatory. This allegation related to Roche's misunderstanding of the meaning of the Eprex SPC at the time the promotional piece was produced. Changes to the Eprex SPC followed an extensive regulatory process. The revised SPC dated July 2002 stated in Section 4.2, Posology and Method of Administration, 'In patients with chronic renal failure, [Eprex] should be administered by the intravenous route where feasible'. This was not a contraindication of the subcutaneous route. The wording had allowed for, but did not define, circumstances where Eprex might be administered subcutaneously to patients with chronic renal failure. Under a further subheading to this section the revised SPC stated 'In patients on haemodialysis, [Eprex] should be administered by the intravenous route'. Following this, and the previous sentence from the SPC, was a statement which referred prescribers to Section 4.4 of the SPC to give greater clarity to the rationale for this amended advice on route of administration. Section 4.4 stated 'As the PRCA cases are mainly associated with the subcutaneous route of administration, Eprex should be administered to chronic renal failure patients by the intravenous route where feasible'. The use of the words 'feasible' and 'should' were not words of contraindication. Indeed, there was no revision to Section 4.3 of the SPC which listed contraindications. Guidance from the European Commission made clear that the information given in Section 4.3 of an SPC was limited to 'situations where the medicinal product must not be given for safety reasons, ie absolute contraindications'. Section 4.3 of the Eprex SPC (July 2001) did not contraindicate the use of SC Eprex in any subgroup of patients (as implied by Roche). Furthermore, a 'Dear Doctor' letter dated 17 July 2002 advising clinicians in respect of route of administration was headed by the phrase 'Amended advice on route of administration'. The word 'advice' and the revisions of the SPC discussed in the letter were not the result of oversight, but were specific phrases amendments following an extensive, iterative, consultative process, involving all the regulatory authorities within the member states of

Europe. The mandatory changes to the route of administration as implied by Roche reflected its profound misunderstanding of the wording of the Eprex SPC. Ortho Biotech denied a breach of Clause 4.2.

Ortho Biotech denied all allegations made by Roche in respect of this particular piece and also in respect of its broader communications to the nephrology community which had been open, honest, and based on thorough and continued scientific investigation.

PANEL RULING

The Panel noted Ortho Biotech's submission that the document in question was given to health professionals only after they had been taken through a broader document which contained detailed information about the definitions used within the document and also a broader discussion as to the company's approach to understanding the rare phenomena of PRCA. In the Panel's view, however, the document in question was a stand alone item; its content had to comply with the Code regardless of any accompanying document or discussion.

The document in question referred to 'suspected PRCA', 'epoetin-associated PRCA', 'antibody-mediated PRCA' and 'loss of clinical response'. The Panel noted that Ortho Biotech had, within the remit of emerging science, discussed these terms with the regulatory authorities and with clinicians. The document included on page 2 explanations for some of the terms used; 'suspected PRCA', 'BM-confirmed PRCA' and 'Antibody-mediated PRCA'. It appeared that although the terms were being used there was no generally accepted definition for them. The supplementary information to Clause 7.2, emerging clinical or scientific opinion, stated that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner in promotional material. The Panel considered that it was misleading not to have defined all the terms used within the document itself. A breach of Clause 7.2 was ruled in that regard. This ruling was appealed.

The Panel noted that the third bullet point of four beneath the heading of 'What is PRCA' stated 'Recently, physicians began noting rare cases of suspected PRCA in kidney disease patients on erythropoietin products, in particular EPREX'. The following bullet point stated that 'Suspected PRCA has been seen with all major erythropoietic products'. The second and third bullet points, beneath a heading of 'What is antibody-mediated PRCA', read 'Erythropoietin products appear to be less immunogenic than some other protein medicines, but like all administered proteins, they carry a risk of immunogenicity' and 'Antibody-mediated PRCA occurs as a result of an immune response to the protein backbone of recombinant human erythropoietin' respectively. The Venn diagram contained a group labelled 'Epoetin-associated PRCA', there was no subset within that relating only to Eprex-associated PRCA. The Panel considered that although one bullet point referred to the fact that erythropoietin-associated PRCA was noted particularly with Eprex, on balance the document was not sufficiently clear in that regard. There were no details of the incidence of PRCA. Some readers would assume that PRCA was equally associated with all erythropoietin products and this was not so. The Panel ruled breaches of Clauses 7.2 and 7.4 of the Code. These rulings were appealed.

The document in question was headed 'What is PRCA?'; the document was not about Eprex and PRCA *per se*. Some weeks before issuing the document Ortho Biotech had issued a 'Dear Doctor' letter about Eprex and PRCA in which it had given amended advice on route of administration and reminded readers about storage conditions. (These had been the subject of a previous complaint, Case AUTH/1399/12/02, which at the time had not yet completed.) The Panel did not consider that the purpose of the document now at issue was such that it should also have contained the information given in the 'Dear Doctor' letter. The Panel did not consider that in omitting information about the safety profile of Eprex the document in question was misleading. The document was about PRCA generally and not about the safety profile of Eprex in particular. No breach of Clause 7.9 was ruled. This ruling was not appealed.

The Venn diagram in the top right-hand corner of the document depicted three sets: 'Loss of Clinical Response' formed the largest circle; 'Suspected PRCA' was depicted as a small subset within 'Loss of clinical response' and 'Epoetin-associated PRCA' was a small subset within 'Suspected PRCA'. Venn diagrams were a way of depicting sets and relationships. The Panel noted that Ortho Biotech had not calculated the area of the circles; in the Panel's view readers would assume that the relative size of each circle bore some relationship to the relative incidence of each subset shown. Using the area of the circles Roche had calculated the relative incidences of loss of clinical response: suspected PRCA: epoetin-associated PRCA to be 138:12:1. The smallest subset was 'Epoetin-associated PRCA' which, in the Panel's view, in the absence of another subset labelled 'Eprex-associated PRCA', implied that PRCA occurred equally with all epoetins which was not so. The Panel noted that route of administration also affected the incidence of PRCA in Eprex-treated patients; PRCA was more likely to occur if renal patients were given subcutaneous Eprex than if the medicine was administered intravenously. Overall the Panel considered that the Venn diagram was too simplistic; it did not convey the issue of PRCA and epoetin therapy with accuracy. A breach of Clause 7.8 was ruled. This ruling was appealed.

The Panel considered that although the diagram gave the misleading impression that PRCA was equally associated with all erythropoietins, it did not downplay the incidence of Eprex-associated PRCA. No breach of Clause 7.9 was ruled in that regard. The Panel, further, did not consider that the diagram disparaged NeoRecormon or any other epoetin. No breach of Clause 8.1 was ruled. Neither of these rulings was appealed.

The Panel noted that under the heading of 'Dosage and administration' the prescribing information stated

that adult chronic renal failure patients on dialysis should receive Eprex 'IV [intravenously] where feasible; if not consider risk/benefit of SC route'. The corresponding section of the SPC (dated July 2002) Section 4.2 stated that 'In patients with chronic renal failure the product should be administered by the intravenous route where feasible' and 'In patients on haemodialysis [Eprex] should be administered by the intravenous route'. Readers of the SPC were referred to Section 4.4, Special Warnings and Precautions for use, regarding PRCA where it was stated that Eprex should be administered to chronic renal failure patients by the intravenous route where feasible. The Panel considered that it was inaccurate to state with regard to chronic renal failure patients on dialysis 'IV where feasible' in the prescribing information given the corresponding statement in the SPC. It appeared that Ortho Biotech had incorporated information from Section 4.4 of the SPC into the statement about dosage and administration in the prescribing information. The Panel thus considered that the statement in the prescribing information was not a succinct statement of the information in the SPC with regard to dosage and method of use as described in Clause 4.2 of the Code. Clause 4.1 of the Code required that the information listed in Clause 4.2 be provided. Failure to do so would therefore be a breach of this clause and not of Clause 4.2. The Panel thus ruled a breach of Clause 4.1 of the Code. This ruling was not appealed.

APPEAL BY ORTHO BIOTECH

Ortho Biotech stated that given the breadth of the issues that had been highlighted in this document (and other documents brought before the Authority in respect of promotion of both NeoRecormon and Eprex) it was clear that one single document could not contain all the facts. Therefore in presenting succinct and key elements of PRCA, careful account must be taken of the audience. Ortho Biotech was careful not to distribute this to a broad section of the medical community (in whom the contents would not be understood and therefore would have the potential to confuse or mislead), but had focussed on the nephrology community, which in the 6 to 8 months prior to this document being used had had extensive communication from Ortho Biotech and would be well aware of the issue of PRCA in association with the use of Eprex. Ortho Biotech agreed that the item should be a stand alone item under the Code, and suitable for the intended audience. The nephrology community had a much higher background level of knowledge of these issues than a practitioner in another speciality. Ortho Biotech submitted that the contents were appropriate for the audience.

Ortho Biotech submitted that although Roche might not be familiar with the terms suspected PRCA, loss of clinical response, etc, the nephrology community certainly was. Indeed 'loss of clinical effect' and 'suspected PRCA' were used in the regulatory approved 'Dear Doctor' letters which were issued through Ortho Biotech on behalf of the MCA and other European Agencies in November 2001 and July 2002. That the regulatory authorities deemed use of these terms appropriate supported the contention that not only were the authorities content with their use in clinical practice but also that they would be understood by the recipients of the letters. Subsequent to the distribution of these two 'Dear Doctor' letters, Ortho Biotech had been in constant communication with the nephrology community and had discussed PRCA and the reporting nomenclature at length, hence these terms would be understood by the target audience. Additionally, terms such as 'suspected' were well known in pharmacovigilance parlance and 'loss of effect' was clinically obvious when using a medicine such as an erythropoietin to maintain a haemoglobin. Ortho Biotech therefore assumed knowledge consistent with the target audience's speciality, and also consistent with the prevalent topics of interest to that community at the time (ie PRCA) and therefore deemed it unnecessary to repeat such definitions within the document.

Ortho Biotech noted that the supplementary information to Clause 7.2, under emerging clinical scientific opinion, stated that when an issue had not been resolved in favour of one generally accepted viewpoint, particular care must be taken to ensure that the issue was treated in a balanced manner. Not defining terms which were in general use for a particular healthcare community did not in any way impair the balance of discussion. It did not change the fact that a greater number of cases of PRCA had been associated with Eprex and that cases of PRCA had been associated with all major erythropoietic products. The debate here was with regard to a comparison or otherwise of the incidence of this adverse event with the individual products, and as argued this was not appropriate.

Ortho Biotech submitted that the inclusion of specific definitions would not alter the comparison between incidence of these products and hence by not including the definitions it had not misled. Ortho Biotech therefore denied a breach of Clause 7.2.

Ortho Biotech noted that the document was divided into two distinct parts. The first under the heading 'What is PRCA?' and the second being 'What is antibody-mediated PRCA?'. Under the heading 'What is PRCA?' there were four bullet points, the first explaining what PRCA was from a haematological perspective and the second stating that PRCA had been associated with certain diseases or treatment. The reader was then referred to a reference at the foot of the page which gave a long list of diseases and medicines with which PRCA was associated. There was a long list of associated causes of PRCA, hence a reader should be aware that in considering a cause of PRCA they should look further afield than purely an association with Eprex or indeed any other erythropoietin.

Ortho Biotech submitted that the third bullet point alluded to the fact that physicians had recently begun to note rare cases of suspected PRCA in renal patients on erythropoietins and in particular Eprex. Given that the first recorded case of PRCA was in 1922 and the extensive other causes/conditions with which PRCA had been associated as outlined in the document, the fact that since about 1998 there had been an increase in the amount of reporting of suspected PRCA cases in patients receiving Eprex,

and that following two 'Dear Doctor' letters (November 2001 and July 2002) again supported how recently it was that physicians began to notice these events.

Ortho Biotech submitted that the three bullet points described above were in a systematic and logical order and all factually correct. A fourth bullet point stating that suspected PRCA had been seen with all major erythropoietin products was also factually correct. This particular article was not specifically about comparison of incidence, however, the third bullet point which stated that suspected PRCA had been noted with erythropoietin products 'in particular Eprex' emphasized that the problem was more prevalent with Eprex than other erythropoietins. In this respect the fourth bullet point did not stand alone and having read the three bullet points in succession, a reader would conclude that suspected PRCA in kidney disease patients was associated more with Eprex than other erythropoietins. Given the extensive degree of communication it was inconceivable that such health professionals were not aware that Eprex had reported most cases. The fourth bullet point did not suggest equality of numbers with Eprex or any of the other erythropoietins and consequently did not breach Clauses 7.2 or 7.4.

With regard to the Venn diagram Ortho Biotech submitted that 'loss of clinical response' might be due to a variety of reasons, the commonest being iron deficiency, infection or lack of compliance. Indeed a loss of clinical response or inappropriate response to an erythropoietin was sufficiently common as to have a European working practice guideline on how to manage it. Once the more common causes of loss of clinical response had been eliminated, clinicians were left with those rarer cases where they suspected PRCA to be the cause. Careful investigation of these cases revealed that a small number which met the clinical criteria for PRCA also had an anti-erythropoietin antibody detectable in their sera.

Ortho Biotech noted that at the time the document was produced PRCA was a much discussed topic amongst the nephrology community and hence there was a heightened degree of reporting of suspected cases. Given the fact that a large number of factors might be associated with PRCA, it was not surprising that cases where anti-erythropoietin antibodies were detectable ie cases of antibody mediated PRCA, remained, despite heightened awareness, rare. A review of a database of chronic renal failure patients, where neither Eprex or NeoRecormon was available, helped to give a clear picture of this. In the US epoetin alfa (marketed as Epogen) was until recently almost exclusively the only erythropoietin available for the management of the anaemia of renal failure. Epogen contained human serum albumin as a stabiliser and was predominantly administered IV. There were, however, a small number of cases of antibody mediated PRCA in the US. A retrospective review of the US data on 154,000 patients with chronic renal failure revealed that refractory anaemia was not uncommon and when cases which might be related to common causes such as iron deficiency, infection etc were excluded the number of cases of profound anaemia (as indicated by a transfusion dependency) that would fit the criteria for suspected PRCA, was 20-30 times higher than the expected background incidence for PRCA. Ortho Biotech submitted that within an environment such as the UK where there was a heightened awareness of PRCA one would expect the number of reported cases of 'suspected PRCA' to be higher than a natural background incidence would suggest. Consequently, although precise figures had not been included in the Venn diagram, it did not distort the low incidence of PRCA (or exaggerate the reporting prevalence of suspected PRCA) or underplay its importance. Thus, in spite of all the activity around PRCA, and in an exhaustive attempt to define the pathogenesis in relationship to antibody mediated PRCA associated with Eprex, PRCA nevertheless remained rare. The Panel noted that there was no comparison of the incidence within the Venn diagram of antibody mediated PRCA associated with Eprex or other erythropoietins. As mentioned previously, it was not appropriate to undertake such comparisons as there was a lack of formal epidemiology data and no direct comparison between the two products. Ortho Biotech emphasized that it was not possible for it to estimate the incidence associated with other products since accurate data regarding incidence or numbers of cases associated with other erythropoietins were not always available. Ortho Biotech therefore submitted that its Venn diagram was accurate and was not misleading, and hence denied breaches of Clauses 7.2 and 7.4 and 7.8.

In summary Ortho Biotech denied that the document was misleading or unbalanced in respect of PRCA and had not implied that erythropoietin associated PRCA was equal in all cases. Indeed, in this matter it was stated that such associations occurred in particular with Eprex. The piece was not about comparison of incidence of PRCA between erythropoietins but was a broader discussion as to the possible pathogenesis of antibody mediated PRCA associated with erythropoietins.

The UK nephrology community was well versed in matters of PRCA and the nomenclature used was consistent with communications to that particular group and appropriate for it. This group was also aware that there were a greater number of cases associated with Eprex than any other erythropoietin, and in respect of this it was not considered necessary to repeat numerically the number of reports associated with Eprex. Furthermore, any comparison of incidence of PRCA between erythropoietins was not appropriate for the arguments which had been laid out within this document.

COMMENTS FROM ROCHE

Roche alleged that Ortho Biotech was wrong to state that the nephrology community in the UK was well versed with the nomenclature used in the document. At the time of the document there were no generally accepted definitions for 'suspected PRCA', 'epoetin-associated PRCA', 'antibody mediated PRCA', and 'loss of clinical response' and there had been no Ortho Biotech communications that had defined these terms to appropriate health professionals. Roche alleged that it seemed contradictory, therefore, that Ortho Biotech, in its appeal, on the one hand defended the

need not to define undefined terms whilst on the other it asserted its intention to seek open communication to the nephrology community. Roche remained convinced that the text by the bullet points was designed to confuse and this was, indeed, the Panel's finding.

Roche alleged that the Venn diagram was similarly confusing. Roche referred to its original complaint and the Panel's ruling. Ortho Biotech's submission that precise figures could not be included again seemed at odds with the statement that Ortho Biotech had been consistent in its open communication to the nephrology community in respect of the number of cases associated with Eprex use. Roche noted the key word here – 'numbers'. What was represented was simplistic and unrepresentative.

Roche remained very concerned about the Eprex campaign, which deliberately sought to lessen the commercial impact of the enforced label change. Ortho Biotech's continual reference to 'erythropoietin products' reduced confidence in all erythropoietins, when the recent epidemic of PRCA referred only to Eprex.

Roche alleged that the commercial interests of Ortho Biotech appeared to outweigh the interests of patients who might be put at unnecessary risk either through inappropriate use or compromise of venous access; lose the opportunity to self-medicate or be denied access to treatment through diminution of confidence in erythropoietins or the increased costs of intravenous therapy. Ortho Biotech's strategy also sought to damage the predominantly subcutaneous market for NeoRecormon.

Roche submitted that the upheld complaints in Case AUTH/1399/12/02, which were of a similar nature, reinforced the Panel's position in this case.

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Prior to consideration of the appeal it had come to the Authority's attention that three versions of the material at issue had been supplied. These were similar but were not identical. The Panel had made the first ruling appealed in relation to the failure to define all the terms used within the document itself, based on one page of the document provided by Roche and one page of the document supplied by Ortho Biotech. The appeal was considered in relation to the one page version supplied by Roche with its original complaint.

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APPEAL BOARD RULING

The Appeal Board noted Ortho Biotech's submission that the document in question would only be provided after the recipient had been taken through a broader document entitled 'Pure Red Cell Aplasia – Background Information' and also a broader discussion as to Ortho Biotech's approach to understanding PRCA. Roche stated that the document had appeared at Ortho Biotech's stand at a meeting in London in October 2002. The Appeal Board considered that the document had to be considered as a stand alone item.

The document referred to 'Suspected PRCA', 'Epoetin-associated PRCA', 'antibody-mediated PRCA' and 'Loss of clinical response'. The Appeal Board considered that the highly specialised audience would be familiar with the issues involved in PRCA and hence would have been familiar with the terms used in the document. The Appeal Board did not consider that it was misleading not to have defined all the terms used within the document itself. The Appeal Board ruled no breach of Clause 7.2. The appeal on this point was successful.

The Appeal Board noted Roche's submission that the SPC for NeoRecormon stated that 'in very rare cases, neutralising anti-erythropoietin antibodies with or without pure red cell aplasia (PRCA) occurred during rHuEPO therapy', whereas the Eprex SPC stated that 'Pure red cell aplasia (erythroblastopenia) has rarely been reported in chronic renal failure patients after months to years of treatment with Eprex or other erythropoietins'.

The Appeal Board noted that the third bullet point of four beneath the heading 'What is PRCA' stated 'Recently, physicians began noting rare cases of suspected PRCA in kidney disease patients on erythropoietin products, in particular Eprex'. The following bullet point stated that 'Suspected PRCA has been seen with all major erythropoietic products'. The second and third bullet points, beneath a heading of 'What is antibody-mediated PRCA', read 'Erythropoietin products appear to be less immunogenic than some other protein medicines, but like all administered proteins, they carry a risk of immunogenicity' and 'Antibody-mediated PRCA occurs as a result of an immune response to the protein backbone of recombinant human erythropoietin' respectively. The Venn diagram contained a set labelled 'Epoetin-associated PRCA', there was no subset within that relating only to Eprex-associated PRCA. The Appeal Board considered that although one bullet point referred to the fact that erythropoietin-associated PRCA was noted particularly with Eprex, on balance the document was not sufficiently clear in that regard. Some readers would assume that PRCA was equally associated with all erythropoietin products and this was not so. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.4 of the Code. The appeal on this point was unsuccessful.

The Venn diagram in the top right-hand corner of the document depicted three sets: 'Loss of clinical response' formed the largest circle; 'Suspected PRCA' was depicted as a small subset within 'Loss of clinical response' and 'Epoetin-associated PRCA' was a small subset within 'Suspected PRCA'. The smallest subset was labelled 'Epoetin-associated PRCA' which, in the absence of another subset labelled 'Eprex-associated PRCA', implied that PRCA occurred equally with all epoetins which was not so.

The Appeal Board noted that at the appeal hearing Ortho Biotech submitted an extract from a detail aid/background document which the company

representatives stated had been used by representatives before using the document at issue. The detail aid/background document gave the numbers of the suspected, confirmed and antibody mediated cases of PRCA for Eprex, Procrit/Epogen, NeoRecormon and Aranesp. The number of cases for Eprex were 141 suspected, 114 confirmed and 66 antibody mediated. The totals for all four products were 159 suspected cases, 128 confirmed cases and 71 antibody mediated cases. The Appeal Board noted that Ortho Biotech had confirmed that the terms 'Epoetin associated PRCA' and 'Antibody mediated PRCA' were to be considered synonymous. Overall the Appeal Board considered that the Venn diagram was too simplistic; it did not convey the issue of PRCA and epoetin therapy with accuracy. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.8. The appeal on this point was unsuccessful.

Complaint received **4 February 2003**

Case completed **22 July 2003**

CASE AUTH/1417/2/03

WYETH v NOVO NORDISK

Promotion of Kliovance

Wyeth complained about the promotion of Kliovance (oestradiol/norethisterone acetate), a continuous combined hormone replacement therapy, by Novo Nordisk. The materials at issue were a leavepiece for the new Kliovance pack, a Novo Nordisk HRT portfolio leavepiece, a MIMS prescribing notes fact pack: HRT 2003, the 'Pause for thought' patient magazine: issue 4, Spring 2002, and a Kliovance for amenorrhoea in HRT leavepiece. Wyeth supplied Premique (conjugated oestrogens/medroxyprogesterone acetate).

The front page of the leavepiece for the new Kliovance pack read 'Kliovance now with improved, easier to use compact' around a visual of a Kliovance calendar dial pack. The calendar dial pack fitted inside what looked like a lady's powder compact.

Wyeth alleged that the word 'new' in the phrase 'The new user-friendly compact…' had been used for more than 12 months.

The Panel noted that the product had been launched in February 2002. The leavepiece had been withdrawn in May 2002. Novo Nordisk could have used the word new 12 months from the launch date. The Panel ruled no breach of the Code.

The Novocare Menopause Support Programme was referred to in the leavepiece and details of the Novo Nordisk Menopause Support Programme, available for all women starting on Novo Nordisk HRT products, was given in a six page HRT portfolio leavepiece. Wyeth alleged that the failure to separate provision of educational services from product promotion constituted an inducement to prescribe.

The Panel noted that the support programmes were designed for the use and benefit of patients; they were not provided as a medical or educational good or service to health professionals. The reply paid card on the leavepiece for the new Kliovance pack enabled health professionals to request items in the Novocare Menopause Support Programme so that they could familiarize themselves with items which might be used by patients. As a result of the service no gift, benefit in kind or pecuniary advantage was offered or given to members of the health professions as an inducement to prescribe, supply or administer Kliovance contrary to the requirements of the Code. No breaches of the Code were ruled in respect of both leavepieces.

The front cover of the fact pack was headed 'MIMS, monthly index of medical specialities, prescribing notes fact pack' in which were held five A5 cards on various topics related to the menopause. Beneath the phrase HRT 2003 in a highlighted box appeared five prescribing recommendations related to each one of the topics on the A5 cards. The back cover of the fact pack bore an advertisement featuring the claims 'When it comes to HRT therapy – not all products are the same'. 'High compliance', 'Low dose', 'Low dose, period free Kliovance'. The corporate logo appeared in the top right hand corner above 'Being there' and the website address.

Wyeth alleged that there was no declaration of sponsorship. Wyeth assumed that the advertisement on the back cover was an abbreviated advertisement as there was no prescribing information.

The Panel considered that the front cover of the fact pack should have contained a declaration of sponsorship. Each fact sheet and the cover would be treated as a stand alone item and thus each item had to comply with the Code. The fact pack cover could thus not take the benefit of a declaration of sponsorship on a separate fact sheet within. A breach of the Code was ruled.

The Panel noted that the abbreviated advertisement appeared on the back of the fact pack. Given Novo Nordisk's submission about the creation and distribution of the fact pack, the Panel considered that in relation to the inclusion of abbreviated advertisements it was not a professional publication of the type envisaged by the Code. The Panel considered that the material failed to meet the requirements of the Code for abbreviated advertisements. Prescribing information was needed and as this had not been included a breach of the Code was ruled.

Wyeth further alleged that the unreferenced strapline 'When it comes to HRT therapy – not all products are the same' was ambiguous and misleading. Wyeth's main concern was that Novo Nordisk was trying to differentiate its products and capitalise on clinicians' concerns about the safety of HRT following publication, in July 2002, of negative safety data for the conjugated oestrogen preparation Prempro; Kliovance by contrast contained oestradiol. In the light of Committee on Safety of Medicines guidance that the safety implications arising from the study should be viewed as a class effect for all HRT preparations (and forthcoming labelling to this effect from the MCA), Wyeth alleged that the strapline 'not all products are the same' was highly misleading and of particular concern as it alluded to patient safety and/or was likely to be interpreted as such. At best the claim was ambiguous, as it was unclear what it meant.

The Panel did not consider that the claim '… not all products are the same' would be read as a claim for superiority, generally, or in relation to safety issues as alleged, nor did the Panel consider it misleading. The Panel considered that the claim would be read in the light of the qualities mentioned in the advertisement in relation to compliance, dose and bleeding. No breach of the Code was ruled.

Wyeth stated that the 'Pause for thought' magazine for patients which was available on the Novo Nordisk website, contained a Kliovance packshot together with the statement that it was 'easier to use'. This was alleged to constitute promotion to the general public and encourage patients to ask their doctor for a specific medicine.

The Panel noted that the magazine was distributed to patients on Novo Nordisk HRT products; it had also been available on Novo Nordisk's open access corporate website. A picture of a blue circular calendar pack containing tablets appeared in the journal alongside text which stated that the company was making circular HRT calendar packs easier to use and continued 'New packs, pictured here, are being introduced for some HRTs from the beginning of this year'.

The Panel noted that out of the whole of Novo Nordisk's oral HRT range only Kliovance was supplied in a blue circular pack. The Panel considered that the depiction of a blue calendar pack on an open access website meant that the picture and associated text referring to HRT constituted an advertisement for a prescription only medicine to the general public and would encourage members of the public to ask for a specific product. Breaches of the Code were ruled.

In relation to the journal's distribution to patients, the Panel noted that patients would already have been prescribed one of Novo Nordisk's HRT products. In April 2002 the circular pack was available for Trisequens, Trisequens Forte, Kliofem and Kliovance and according to the article would be made available for all HRT tablet presentations that year. The Panel also noted the products' differing indications. In such circumstances the Panel did not consider that the depiction of the Kliovance calendar pack and the accompanying text would encourage patients on other Novo Nordisk HRT products to seek a prescription for Kliovance. No breach of the Code was ruled.

Wyeth alleged that the strapline in a leavepiece 'For amenorrhoea in HRT' was ambiguous and misleading because it implied that amenorrhoea was certain and complete with Kliovance.

The Panel noted that Kliovance was a continuous combined HRT indicated for oestrogen deficiency symptoms in women who were more than one year past the menopause and for prevention of osteoporosis in postmenopausal women. Such women would have no monthly bleeding before starting Kliovance. Section 4.8 of the summary of product characteristics (SPC) stated that 'Breakthrough bleeding and spotting often occur during the initial months of treatment'. Section 4.8 Undesirable effects stated that, *inter alia*, vaginal bleeding had been associated with Kliovance during clinical trials. The Panel considered that the claim 'For amenorrhoea in HRT' gave the impression that amenorrhoea was certain and complete; that was not so. A breach of the Code was ruled.

Wyeth noted that the leavepiece included a bar chart which directly compared Kliovance and Premique for percentage of amenorrhoeic patients after 2 months, despite the fact that the results were from two different studies. This was alleged to be inappropriate for obvious reasons, including differences in patient population, inclusion criteria, the definition of amenorrhoea (eg how many episodes of spotting were allowed), and other methodological differences.

Wyeth questioned the use of the term 'amenorrhoea' (ie no bleeding or spotting) for the Kliovance data, and believed it should be 'no bleeding' (ie including spotting), which was the term used in the study cited. Although this issue had been the subject of Case AUTH/1235/10/01 in which no breach of the Code had been ruled, new data had come to light. In Johnson *et al* (2002) data for 'no bleeding' and 'no bleeding and no spotting' (ie amenorrhoea) were presented for Kliovance cycles 1-3; the 'no bleeding' rate was 76.5%, very similar to the 73% quoted for Kliovance after 2 months by Archer *et al* (1999) but the amenorrhoea rate was only 58.5%. Wyeth submitted that this additional information supported its argument in Case AUTH/1235/10/01 that the 73% was 'no bleeding' and not 'amenorrhoea'.

Even if one accepted 73% was amenorrhoea, this was a selection of the best data (ie 73% instead of 58.5%) which was misleading and not a fair comparison with Premique. At the very least, a range of reported amenorrhoea rates for the same product also illustrated why a head-to-head comparison with Premique and Femoston-Conti using data from 3 different trials was flawed and inaccurate; directly comparing amenorrhoea results from different trials with different methodologies was completely untenable.

The Panel noted that the bar chart depicted the percentage of amenorrhoeic patients after two

months for Kliovance (73%; n=295), Premique (57%; n=338) and after six months for Femoston-conti (72%; n=160), referenced to Archer *et al* (1999), Archer *et al* (1994) and Solvay promotional material respectively. An asterisk adjacent to the heading, 'Reported bleed data for continuous-combined HRT' referred the reader to a footnote, immediately beneath the bar chart, which read 'Data from 3 different trials'.

Archer *et al* (1999) was a prospective double blind randomized trial on 1176 healthy postmenopausal women aged 45 years and older (mean 56 years) assigned to assess the bleeding profile of Kliovance. Bleeding data for each day was recorded as either no bleeding or spotting, bleeding, or spotting. The Panel considered it was clear from the definitions given by Archer *et al* that no bleeding meant no release at all of uterine blood ie no bleeding or spotting. The results showed that 72.7% of patients on Kliovance had no bleeding at cycle two. The Kliovance patients n=295 had a mean age of 56 years and at baseline had been period free for a mean of 7 years.

The Premique data was referenced to Archer at al (1994) which assessed the bleeding patterns in 1724 postmenopausal women taking two continuous combined and two sequential regimens of conjugated oestrogens and medroxyprogesterone acetate and conjugated oestrogens alone. Three hundred and thirty eight patients were randomized to the Premique group, their mean age was 54 years and the mean time since last menses was 5.3 years. Bleeding and spotting were defined in patients' diary cards as vaginal bleeding that did or did not, respectively, require sanitary protection. For the analysis of data amenorrhoea was defined as the absence of any bleeding or spotting during the entire 28 day medication cycle.

The Panel noted that the definition of amenorrhoea in Archer *et al* (1994) was similar to that of 'no bleeding' in Archer *et al* (1999). There were however differences in patient population, inclusion criteria and methodology. The Panel considered that the depiction of the data within the same bar chart beneath the heading 'Reported bleed data for continuous-combined HRT' invited the reader to directly compare the data and implied that it was valid to do so; the footnote did not negate the overall impression given. The bar chart was misleading in this regard. Breaches of the Code were ruled.

The Panel noted that Wyeth questioned the use of the term 'amenorrhoea' in relation to the Kliovance data. Reference was made to Case AUTH/1235/10/01 which concerned a Kliovance leavepiece wherein Wyeth had alleged that the use of the word 'amenorrhoea' in a claim for Kliovance referenced to Archer *et al* (1999), could not be justified due to the level of ambiguity and lack of clarity in Archer *et al* (1999) about the term no bleeding. The Panel noted the definitions of the terms used by Archer *et al* and considered that the term 'no bleeding' was effectively amenorrhoea. The Panel had considered that use of the term amenorrhoea could thus be justified and was thus not misleading as alleged. No breach of the Code had been ruled.

Turning to the present case, Case AUTH/1417/2/03, the Panel noted that Wyeth similarly queried the use of the term amenorrhoea to describe the Kliovance data from Archer *et al* and on this narrow point considered that its ruling in Case AUTH/1235/10/01 was relevant and ruled no breach of the Code.

In relation to the allegation that 73% was not a fair reflection of the evidence, the Panel noted that the figure of 58.5% for the percentage of patients who experienced no bleeding and no spotting during Kliovance cycles 1-3 in Johnson *et al* was markedly different to that depicted in the bar chart. The Panel noted that the data in the leavepiece at issue depicted the incidence of amenorrhoea and considered that given Johnson *et al* it was no longer a fair reflection of the balance of the evidence on this point. A breach of the Code was ruled.

Upon appeal by Novo Nordisk, the Appeal Board noted that Archer *et al* had reported that 73% of women were amenorrhoeic on Kliovance at month 2 of treatment. Von Holst *et al* had reported that 86.3% of women on Kliovance had no irregular bleeding at 3 months and a figure of 75% of women reporting amenorrhoea at 2 months on Kliovance could be approximated from a graph in Stadberg *et al*.

The Appeal Board noted Novo Nordisk's comments about the misunderstanding of the Johnson *et al* study. The published data referred to a cumulative incidence for 3 separate months (58.5%) and not a point incidence (73%) as in Archer *et al*. The Appeal Board noted a retrospective analysis of the unpublished data from Johnson *et al* had shown that in women less than three years from the menopause, 73% had reported amenorrhoea at month 2 on Kliovance; in women more than three years since the menopause the comparable figure was 70%. Further retrospective analysis from the unpublished von Holst *et al* data had shown that 80.8% of women were amenorrhoeic at month 2 on Kliovance although this figure was disputed by Wyeth at the appeal as it considered that it represented per protocol data as opposed to intent to treat data. Wyeth contended that the figure for intent to treat at month 2 would be lower; this point was accepted by Novo Nordisk.

The Appeal Board queried the validity of retrospective analyses of unpublished data. The Appeal Board considered that 73% of women reporting amenorrhoea at month 2 on Kliovance was a fair reflection of the available published evidence. Archer *et al* was a large trial, the unpublished data from other studies cited by Novo Nordisk was not inconsistent with Archer *et al*. The Appeal Board ruled no breach of the Code.

Wyeth Pharmaceuticals complained about the promotion of Kliovance (oestradiol/norethisterone acetate), a continuous combined hormone replacement therapy, by Novo Nordisk Limited. The materials at issue were a leavepiece (ref KV/01/01) for the new Kliovance pack, a Novo Nordisk HRT portfolio leavepiece (ref KV/02/11), a MIMS prescribing notes fact pack: HRT 2003 (ref KV/02/27), the 'Pause for thought' patient magazine: issue 4,

Spring 2002 (ref KV/02/03) and Kliovance for amenorrhoea in HRT leavepiece (ref KV/02/10). Wyeth supplied Premique (conjugated oestrogens/medroxprogesterone acetate).

1 Circular shaped eight page leavepiece for the new Kliovance pack (ref KV/01/01)

The front page of the leavepiece read 'Kliovance now with improved, easier to use compact' around a visual of a Kliovance calendar dial pack. The calendar dial pack fitted inside what otherwise looked like a lady's powder compact. Page 4 discussed the Novocare Menopause Support Programme and page 5 was a detachable reply paid card whereby the reader could obtain items from the Menopause Support Programme.

COMPLAINT

Wyeth noted that the phrase 'The new user-friendly compact…' was used although this pack had been available for more than 12 months (date of preparation of the leavepiece was almost two years ago; January 2001). A breach of Clause 7.11 of the Code was alleged. Novo Nordisk had admitted that the leavepiece was nearly two years old, but stated that it had not been distributed for some time. Wyeth refuted this, as clearly the item was in circulation if one of its representatives obtained it. Moreover, Novo Nordisk should have proactively ensured that the item was withdrawn from distribution and would no longer be used – it had provided no evidence that this had been done.

With regard to the Novocare Menopause Support Programme, Wyeth alleged that the failure to separate provision of educational services from product promotion – ie both in the same leavepiece – constituted an inducement to prescribe in breach of Clause 18.1. Indeed, the page describing the support programme stated 'So, now there are more reasons than ever before to prescribe Kliovance'.

RESPONSE

Novo Nordisk agreed that the leavepiece was two years old but stated that it had not been distributed for some considerable time. Although the leavepiece was prepared in January 2001 the product launch was delayed until February 2002. Thus the word 'new' would actually still be appropriate under Clause 7.11 of the Code until February 2003. The leavepiece was however withdrawn in May 2002 since new materials were launched at that time. Following the use of new materials, representatives were told not to use any old material, but just in case they had any left an additional email had now been sent reminding them not to use it. Wyeth had not provided any information as to where and when its representative obtained a copy of this leavepiece and so clearly Novo Nordisk could not investigate how it became available. Materials could remain on doctors' shelves for some time however, so it was not surprising that a leavepiece from a year ago had been found at one of Novo Nordisk's customers' sites. Novo Nordisk denied a breach of Clause 7.11 of the Code.

Novo Nordisk noted that Wyeth continued to claim that the NovoCare Menopause Support Programme (now called the Novo Nordisk Menopause Support Programme) was an educational service although it was not intended for health professionals but was a support service for patients who used Novo Nordisk products. Health professionals receiving information about the support programme did not receive any gifts, benefits in kind or pecuniary advantages including educational goods or services as a result of using it and therefore it was not an inducement to prescribe Novo Nordisk's products. Thus the statement 'So, now there are more reasons than ever before to prescribe Kliovance' was never intended as an inducement to prescribe. Novo Nordisk did not agree with Wyeth that it had been in breach of Clause 18.1 of the Code.

PANEL RULING

The Panel noted that Kliovance was presented in a calendar dial pack which fitted into what looked like a lady's powder compact. Page 2 of the leavepiece included the claims 'The new user-friendly compact has been improved to make it safer and easier for patients to operate' and 'The compact remains small and discreet but now comes with a finger grip to set the day reminder, so there's no need to use a coin'. It thus appeared that when Novo Nordisk referred to 'the compact' it was referring to the presentation of Kliovance as opposed to the small carrying case. The Panel noted that Clause 7.11 prohibited the use of the word 'new' to describe any product or presentation which had been available, or any therapeutic indication which had been generally promoted, for more than 12 months in the UK. The Panel noted that the term 'new' in the phrase 'The new user-friendly compact …' was used to describe the compact dial device ie the presentation of Kliovance. Although the claim was in a leavepiece which had been prepared in January 2001 it had not been used until February 2002 as the product had not been launched until then. The leavepiece had been withdrawn from use in May 2002 when new materials had been introduced. Notwithstanding the withdrawal of the leavepiece the claim 'The new user-friendly compact …' could have been used until February 2003 ie for 1 year following the launch of the calendar dial pack. Wyeth had submitted its complaint in February 2003. Novo Nordisk had since emailed its representatives telling them not to use any old materials. The Panel ruled no breach of Clause 7.11 of the Code.

The Panel noted that the NovoCare Menopause Support Programme comprised a video, booklet, interactive CD-ROM, ethnic language information leaflets, a risks and benefits leaflet and a dial pack demonstration kit. Each item was designed for patients, according to the leavepiece, to provide them with 'balanced facts to help them decide how to manage their menopause'. Page 4 of the leavepiece discussed the Novocare Menopause Support Programme and concluded 'So, now there are more reasons than ever before to prescribe Kliovance'.

The Panel noted that the NovoCare Menopause Support Programme was designed for the use and benefit of patients; it was not provided as a medical or

educational good or service to health professionals under the supplementary information to Clause 18.1. The reply paid card on the leavepiece at issue enabled health professionals to request support items in the Novocare Menopause Support Programme so that they could familiarize themselves with items which might be used by patients. Patients would receive the video and compact case by completing a tear-off slip on the patient information leaflet. As a result of the service no gift, benefit in kind or pecuniary advantage was offered or given to members of the health professions as an inducement to prescribe, supply or administer Kliovance contrary to the requirements of Clause 18.1 of the Code. No breach of that clause was ruled.

2 Novo Nordisk HRT portfolio leavepiece (ref KV/02/11)

This six page leavepiece presented five Novo Nordisk hormone replacement therapy (HRT) products. Page 3 gave details of the Novo Nordisk Menopause Support Programme available for all women starting on Novo Nordisk HRT products.

COMPLAINT

Wyeth stated that as with point 1 above, this item linked the Novo Nordisk Menopause Support Programme with product promotion, as both were contained within it. A breach of Clause 18.1 of the Code was alleged.

RESPONSE

Novo Nordisk repeated that the mention of the Novo Nordisk Menopause Support Programme was not an inducement to prescribe since this was a support service for the benefit of patients who used Novo Nordisk products and not an education programme for health professionals or one which offered them gifts, benefits in kind or any pecuniary advantage. Novo Nordisk did not believe that simply mentioning a product support programme in promotional material breached Clause 18.1 of the Code. None of the materials in Novo Nordisk's Menopause Support Programme bore product names, in compliance with Clause 20 of the Code. Patients obtained the materials on offer by completing a tear-off slip on the bottom of the patient information leaflet. The patient video was approved by the Medicines Control Agency (MCA) as part of the package insert for Kliovance since it provided patient information. It was agreed with the MCA that this video was non-promotional and that Novo Nordisk would provide copies to any doctor that wished to see it, whether or not they prescribed Novo Nordisk's products. The video was withdrawn last year, however, after the Women's Health Initiative (WHI) study was published since Novo Nordisk considered it to be inconsistent with the European Mutual Recognition Facilitation Group core summary of product characteristics (SPC) for HRT. The magazine 'Pause for thought' had also now been withdrawn. As a result of the introduction of new material the leavepiece in question was withdrawn in January 2003. Novo Nordisk denied that this leavepiece was in breach of Clause 18.1 of the Code.

PANEL RULING

The Panel considered that its comments at point 1 above about the Menopause Support Programme applied here; accordingly no breach of Clause 18.1 was ruled.

3 MIMS prescribing notes fact pack: HRT 2003 (ref KV/02/27 – July 2002)

The fact pack was a wallet made of card which held five A5 cards on various topics related to the menopause.

The front cover of the fact pack was headed 'MIMS, monthly index of medical specialities, prescribing notes fact pack'. Beneath the phrase HRT 2003 in a highlighted box appeared five prescribing recommendations related to each one of the topics on the A5 cards. The back cover of the fact pack bore an advertisement ref KV/02/27 featuring the claims 'When it comes to HRT therapy – not all products are the same'. 'High compliance', 'Low dose', 'Low dose, period free Kliovance'. The corporate logo appeared in the top right hand corner above 'Being there' and the website address.

COMPLAINT

Wyeth stated that despite an advertisement on the back cover of the fact pack, there was no declaration of sponsorship and alleged a breach of Clause 9.9 [2001 edition]. Novo Nordisk's response referred to the fact that cards were contained within the pack. This was irrelevant as Wyeth's complaint referred to the pack containing the cards, not the cards themselves. Wyeth assumed that the advertisement was an abbreviated advertisement as there was no prescribing information. As such, the inclusion of the claims 'High compliance', 'Low dose' and 'When it comes to HRT therapy – not all products are the same' breached Clause 5.

Wyeth further alleged that the unreferenced strapline 'When it comes to HRT therapy – not all products are the same' was ambiguous and misleading and in breach of Clause 7.2; the claim could be interpreted as implying superiority, for which there was no evidence. In what way were HRT products different, and what was the supportive data? What was meant by this strapline? Novo Nordisk's response did not address these points adequately. Wyeth's main concern was that Novo Nordisk was trying to capitalise on clinicians' concerns about the safety of HRT following publication of the WHI study in early July 2002 – specifically to differentiate itself from it. This was a large US randomised controlled trial which reported negative safety data for the conjugated oestrogen preparation Prempro, and was widely reported in the UK media; Kliovance by contrast contained oestradiol. In the light of Committee on Safety of Medicines (CSM) guidance that the safety implications arising from the WHI study should be viewed as a class effect for all HRT preparations (and forthcoming labelling to this effect from the MCA), Wyeth alleged that the strapline 'not all products are the same' was highly misleading and in breach of Clause 7.3 and of particular concern as it alluded to

patient safety and/or was likely to be interpreted as such. At best the claim was ambiguous, as it was unclear what it meant, and was alleged to be in breach of Clause 7.2.

RESPONSE

Novo Nordisk stated that it was approached by MIMS to sponsor the production of a prescribing notes fact pack on HRT drafted by an independent consultant. Once the fact pack had been drafted, Novo Nordisk put it through its approval process. However the company had no editorial input. There was a statement on the back of the cards in the fact pack confirming this: 'The views expressed in this publication are those of the authors and not necessarily those of Haymarket Medical Imprint or Novo Nordisk Limited'.

The fact pack was advertised by Haymarket Medical Imprint (MIMS' publisher) in some of its other publications eg GP magazine. If doctors requested a copy from Haymarket Medical Imprint their names and addresses were passed to Novo Nordisk and the fact packs were delivered by Novo Nordisk representatives. There was no obligation for doctors to see a representative and the fact packs would have been left for the doctors regardless. Novo Nordisk representatives also had copies of the fact pack which they could provide if they received a direct request.

Novo Nordisk stated that its company logo was included in the advertisement on the back of the pack as was the name and address of the company so it considered that it was obvious that it had sponsored the pack. Each card within the pack contained a clear statement that the cards were 'provided as a service by Novo Nordisk', alongside the Novo Nordisk logo. The advertisement fulfilled the requirements of an abbreviated advertisement. The indication was in the claim 'When it comes to HRT therapy – not all products are the same'. 'High compliance', 'Low dose' were additional concise statements, consistent with the SPC, giving the reason why the product was recommended, as permitted by Clause 5.6. Novo Nordisk denied a breach of Clause 9.9 [2001 edition].

Novo Nordisk did not consider that the strapline 'When it comes to HRT – not all products are the same' was ambiguous and misleading, in breach of Clause 7.2. Given the variety of HRT products on the market (with different medicines, doses, delivery systems and indications etc) Novo Nordisk found it astonishing that Wyeth considered that all HRT products were the same. Nor was there a claim of superiority in this strapline. It was purely a statement of fact. This advertisement did not mention the WHI study; Novo Nordisk submitted that Wyeth was over-reacting to a study that was not in its favour. The strapline did not refer to safety any more than it did to efficacy and Novo Nordisk did not believe it was misleading in any way. It simply stated that not all HRT products were the same. Novo Nordisk did not agree with Wyeth if it was implying that the CSM viewed all HRT as the same when it stated that 'In the light of CSM guidance that the safety implications arising from the WHI study should be viewed as a class effect for all HRT preparations…'. The new European Mutual Recognition Facilitation Group core SPC for hormone replacement therapy had not been approved yet but the proposed wording for coronary artery disease in section 4.4, Special warnings and precautions, was as follows: 'There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined oestrogens and [medroxyprogesterone acetate]. Large clinical trials showed a possible increased risk of cardiovascular morbidity in the first year of use and no benefits thereafter. For other HRT products there are as yet no randomised controlled trials examining benefit in cardiovascular morbidity or mortality. Therefore it is uncertain whether these findings also extend to other HRT products'. Clearly not all HRT products were viewed as being the same by the regulatory authorities. Thus Novo Nordisk did not believe that this advertisement was in breach of Clauses 7.2 and 7.3.

PANEL RULING

The Panel considered that the front cover of the fact pack should have contained a declaration of sponsorship as required by Clause 9.9 (2001 edition). The supplementary information to Clause 9.9 stated that the declaration of sponsorship must be sufficiently prominent to ensure readers of sponsored material are aware of it at the outset. The advertisement on the back cover and the statement on each fact sheet within, 'Provided as a service by Novo Nordisk', were insufficient in this regard. Each fact sheet and the cover would be treated as a stand alone item and thus each item had to comply with the Code. The fact pack cover could thus not take the benefit of a declaration of sponsorship on a separate fact sheet within. A breach of Clause 9.9 (2001 edition) was ruled.

The Panel noted that the abbreviated advertisement appeared on the back of the fact pack. Clause 5.2 stated that abbreviated advertisements could only appear in professional publications ie publications sent or delivered wholly or mainly to members of the health professions. The Panel considered that given Novo Nordisk's submission about the creation and distribution of the fact pack it was not a professional publication of the type envisaged by Clause 5.2 of the Code.

Clause 5.4 required abbreviated advertisements to contain, *inter alia*, at least one indication for use, consistent with the SPC. Clause 5.6 stated that abbreviated advertisements may in addition contain a concise statement consistent with the SPC giving the reason why the medicine was recommended for the indication or indications given. The Panel noted the reference to the indication in the claim 'When it comes to HRT therapy – not all products are the same'. On balance, the Panel considered that the design of the advertisement and juxtaposition of the claims were such that 'High compliance' 'Low dose', 'Low dose, period free Kliovance' were designed to be read as one concise statement giving the reason why the medicine was recommended for the indication given in accordance within Clause 5.6.

Clause 5.1 stated that abbreviated advertisements were exempt from the requirement to include

prescribing information provided they met the requirements of Clause 5. The Panel considered that the material failed to meet the requirements of Clause 5 as alleged, in particular Clause 5.2 and thus prescribing information as required by Clause 4.1 of the Code was needed. A breach of Clause 4.1 was ruled.

The Panel did not consider that the claim '… not all products are the same' either in isolation or within the context of the whole advertisement would be read as a claim for superiority, generally, or in relation to safety issues arising from the WHI study as alleged, nor did the Panel consider it misleading. The Panel considered that the claim would be read in light of the qualities mentioned in the advertisement in relation to compliance, dose and bleeding. No breach of Clauses 7.2 and 7.3 was ruled.

4 'Pause for thought' magazine for patients: Issue 4, Spring 2002 (ref KV/02/03 April 2002)

COMPLAINT

Wyeth stated that this magazine, which was available on the Novo Nordisk website, contained a Kliovance packshot on page 2, together with the statement that it was 'easier to use'. This constituted promotion to the general public in breach of Clause 20.1, and encouraged patients to ask their doctor for a specific medicine in breach of Clause 20.2, particularly as brand names and product information were openly accessible on the website. Novo Nordisk had not accepted a breach of the Code, and yet had modified its website to remove the magazine. Given the clear nature of these breaches, Wyeth was not satisfied with Novo Nordisk's failure to admit fault, and had therefore included this point as part of its complaint.

RESPONSE

Novo Nordisk stated that the Kliovance packshot on page 2 of the magazine did not mention the product name so patients would not be able to ask their doctor for Kliovance by name as a result of seeing this article. The picture was of an unbranded dial pack in which all Novo Nordisk's systemic HRT products were provided. The statement 'easier to use' referred to the use of the calendar pack and not any specific HRT product. Since 'Pause for thought' was only meant for patients on Novo Nordisk products it was an oversight that some issues of the magazine were available on Novo Nordisk's website. Thus although Novo Nordisk did not believe this to be in breach of the Code these issues of the magazine were withdrawn from the website following receipt of Wyeth's letter. Novo Nordisk disagreed that this magazine was in breach of Clauses 20.1 and 20.2.

In response to a request for further information Novo Nordisk stated that as of April 2002 the circular calendar pack was associated with 4 marketed products, Trisequens, Trisequens Forte, Kliofem and Kliovance. The blue colour was only associated with about 50% of packs of Kliovance since at that time 50% of sales were in parallel imports (pink circular pack).

Novo Nordisk noted, however, that no name could be read from the picture; the company submitted that it would be very unlikely that any patient would ask for a 'blue calendar pack of HRT'. It was also likely that most GPs would not know the colour and even if they did there was a high chance of an alternative colour being dispensed. Companies could display products on their open access websites as long as no claims were made for them and indeed no claims were made for Kliovance.

PANEL RULING

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines to the general public and medicines which although not prescription only, might not legally be advertised to the general public. Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine. The Panel noted that the magazine was distributed to patients on Novo Nordisk HRT products; it had also been available on Novo Nordisk's open access corporate website.

A picture of a blue circular calendar pack containing tablets appeared in the journal alongside text which stated that the company was making circular HRT calendar packs easier to use and continued 'New packs, pictured here, are being introduced for some HRTs from the beginning of this year'.

The Panel noted that according to a demonstration pack provided by Novo Nordisk, Kliovance, Kliofem, Novofem and Trisequens were supplied in blue, mauve, turquoise and grey circular packs respectively. The Panel considered that the depiction of a blue calendar pack which was solely associated with the use of Kliovance on an open access website meant that the picture and associated text referring to HRT constituted an advertisement for a prescription only medicine to the general public and would encourage members of the public to ask for a specific product. Breaches of Clauses 20.1 and 20.2 were ruled.

In relation to the journal's distribution to patients the Panel considered that the picture and article were designed to generate interest in the circular calendar pack. Given its colour, the circular pack depicted was that of Kliovance. The Panel noted that patients would already have been prescribed one of Novo Nordisk's HRT products. At April 2002 the circular pack was available for Trisequens, Trisequens Forte, Kliofem and Kliovance and according to the article would be made available for all HRT tablet presentations that year. The Panel also noted the products' differing indications. In such circumstances the Panel did not consider that the depiction of the Kliovance calendar pack and the accompanying text would encourage patients on other Novo Nordisk HRT products to seek a prescription for Kliovance. No breach of Clause 20.2 was ruled.

5 Kliovance – For amenorrhoea in HRT leavepiece (ref KV/02/10)

COMPLAINT

Wyeth alleged that the strapline 'For amenorrhoea in HRT' was ambiguous and misleading because it implied that amenorrhoea was certain and complete with Kliovance. A caveat was surely needed.

On page two a bar chart directly compared Kliovance and Premique for percentage of amenorrhoeic patients after 2 months, despite the fact that the results were from two different studies. This was alleged to be inappropriate for obvious reasons, including differences in patient population, inclusion criteria, the definition of amenorrhoea (eg how many episodes of spotting were allowed), and other methodological differences. For example, the mean age of patients was 54 years in the Premique study and 56 years in the Kliovance study (years since last menses 5.3 years Premique, 7 years Kliovance), and one would expect older women to have a higher baseline level of amenorrhoea. Breaches of Clauses 7.2, 7.3 and 7.8 were alleged.

Wyeth questioned the use of the term 'amenorrhoea' (ie no bleeding or spotting) for the Kliovance data, and believed it should be 'no bleeding' (ie including spotting), which was the term used in the study cited. Although this issue had been the subject of Case AUTH/1235/10/01 in which no breach of the Code had been ruled, new data had come to light. Johnson *et al* (2002) – data for 'no bleeding' and 'no bleeding and no spotting' (ie amenorrhoea) were presented for Kliovance cycles 1-3, the 'no bleeding' rate was 76.5%, very similar to the 73% quoted for Kliovance after 2 months by Archer *et al* (1999) but the amenorrhoea rate was only 58.5%. Wyeth believed this additional information supported its argument in Case AUTH/1235/10/01 that the 73% was 'no bleeding' and not 'amenorrhoea'. Wyeth alleged a serious breach of Clause 7.2.

Even if one accepted 73% was amenorrhoea, this was a selection of the best data (ie 73% instead of 58.5%) which was misleading and in breach of Clause 7.3 and not a fair comparison with Premique in breach of Clause 7.2. At the very least, a range of reported amenorrhoea rates for the same product also illustrated why a head-to-head comparison with Premique and Femoston-Conti using data from 3 different trials was flawed and inaccurate in breach of Clause 7.2. Archer and Pickar (2002) reviewed the assessment of bleeding patterns in postmenopausal women during continuous combined HRT, and stated that 'Inconsistencies among clinical trials in bleeding pattern definitions and indices limit understanding and comparison of typical bleeding patterns with continuous combined HRT regimens'. In other words, expert opinion supported Wyeth's contention that a comparison of amenorrhoea rates from different studies, based on current non-standard methodologies, was not valid. Notably Archer was the lead investigator in the earlier Kliovance trial reporting 73% amenorrhoea (Archer *et al*, 1999) and a co-investigator in the most recent Kliovance trial reporting 58.5% amenorrhoea (Johnson *et al*, 2002), so his comments were highly pertinent to the current complaint. In the light of Archer's comments and reported results, Wyeth considered that the head-to-head comparison of amenorrhoea results from different trials with different methodologies was completely untenable.

RESPONSE

Novo Nordisk stated that the strapline 'For amenorrhoea in HRT' was not a claim but a representation of the reason why prescribers chose to use a continuous combined 'period-free' HRT product; the aim was to achieve amenorrhoea. The strapline did not imply anything other than Kliovance was an HRT product with a good amenorrhoea profile, a claim Novo Nordisk could support. Novo Nordisk denied a breach of Clause 7.2.

Since no head-to-head studies comparing Kliovance with Premique had been conducted it was not possible to give such comparative data. A good bleed profile was important to customers however so Novo Nordisk believed it was appropriate to compare the results from different studies and this fact was not hidden in any way. Novo Nordisk denied breaches of Clauses 7.2, 7.3 and 7.8.

The issue of Kliovance amenorrhoea data was the subject of a previous complaint by Wyeth (Case AUTH/1235/10/01) and the Panel had found that Novo Nordisk's use of the term amenorrhoea was justified. The study by Johnson *et al* that Wyeth now mentioned, compared Kliovance with Prempro. Since Prempro was not available in the UK Novo Nordisk had not used this paper in any of its promotional material as it did not consider the data for this product were relevant here. This paper did not affect the previous decision of the Panel that the figure of 73% amenorrhoea that Novo Nordisk quoted with Kliovance was indeed a figure for amenorrhoea and not a figure for 'no-bleeding' as Wyeth persistently claimed. Novo Nordisk denied a breach of Clause 7.2.

PANEL RULING

The Panel noted that the front page of the leavepiece was headed 'Kliovance – For amenorrhoea in HRT' a strapline read 'Low dose, period free'. The claim also appeared as a bullet point on the final page. 'Amenorrhoea in HRT' headed page two. The Panel noted that Kliovance was a continuous combined HRT indicated for oestrogen deficiency symptoms in women who were more than one year past the menopause and for prevention of osteoporosis in postmenopausal women. Such women would have no monthly bleeding before starting Kliovance. Section 4.4 of the SPC stated that 'Breakthrough bleeding and spotting often occur during the initial months of treatment'. Section 4.8, Undesirable effects, stated that, *inter alia*, vaginal bleeding had been associated with Kliovance during clinical trials. The Panel considered that the claim 'For amenorrhoea in HRT' gave the impression that amenorrhoea was certain and complete; that was not so. A breach of Clause 7.2 was ruled.

The Panel noted that the bar chart at issue on page two depicted the percentage of amenorrhoeic patients

after two months for Kliovance (73%; n=295), Premique (57%; n=338) and after six months for Femoston-conti (72%; n=160) referenced to Archer *et al* (1999), Archer *et al* (1994) and Solvay promotional material FEM166 respectively. An asterisk, adjacent to the heading 'Reported bleed data for continuous-combined HRT' referred the reader to a footnote, immediately beneath the bar chart which read 'Data from 3 different trials'.

Archer *et al* (1999) was a prospective double blind randomized trial on 1176 healthy postmenopausal women aged 45 years and older (mean 56 years) assigned to assess the bleeding profile of Kliovance. Bleeding data for each day was recorded as either no bleeding or spotting, bleeding, or spotting. Bleeding was defined as release of uterine blood that required sanitary protection, while spotting was defined as release of uterine blood that did not require sanitary protection. A bleeding episode was defined as a period of one or more consecutive days of bleeding or spotting separated by at least 1 day of no bleeding or spotting. All months were classified into one of three categories; month with no bleeding, month with bleeding (with or without spotting) or month with spotting only (no bleeding). The Panel considered it was clear from the definitions given by Archer *et al* that no bleeding meant no release at all of uterine blood ie no bleeding or spotting. The results showed that 72.7% of patients on Kliovance had no bleeding at cycle two. The Kliovance patients n=295 had a mean age of 56 years and at baseline had been period free for a mean of 7 years. The study authors stated that the effect of the norethisterone acetate dose on bleeding appeared to be greater when the last menses occurred less than 3 years before initiation of therapy and concluded that the study findings supported the use of continuous combined formulas with a relatively higher progestogen dose in women who initiated treatment closer to the menopause.

The Premique data was referenced to Archer *et al* (1994) which assessed the bleeding patterns in 1724 postmenopausal women taking two continuous combined and two sequential regimens of conjugated oestrogens and medroxyprogesterone acetate and conjugated oestrogens alone. Three hundred and thirty eight patients were randomized to the Premique group, their mean age was 54 years and the mean time since last menses was 5.3 years. Bleeding and spotting were defined in patients' diary cards as vaginal bleeding that did or did not, respectively, require sanitary protection. For the analysis of data amenorrhoea was defined as the absence of any bleeding or spotting during the entire 28 day medication cycle.

The Panel noted that the definition of amenorrhoea in Archer *et al* (1994) was similar to that of 'no bleeding' in Archer *et al* (1999). There were however differences in patient population, inclusion criteria and methodology. The Panel considered that the depiction of the data within the same bar chart beneath the heading 'Reported bleed data for continuous-combined HRT' invited the reader to directly compare the data and implied that it was valid to do so; the footnote did not negate the overall impression given. The bar chart was misleading in this regard. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

The Panel noted that Wyeth questioned the use of the term 'amenorrhoea' in relation to the Kliovance data. Reference was made to Case AUTH/1235/10/01 which concerned a Kliovance leavepiece wherein Wyeth had alleged that the use of the word 'amenorrhoea' in the claim '73% of women can expect to be amenorrhoeic as early as 8 weeks from start of treatment' and a figure depicting the percentage of women amenorrhoeic at 2, 6 and 11 months, referenced to Archer *et al* (1999), could not be justified due to the level of ambiguity and lack of clarity in Archer *et al* (1999) about the term no bleeding. The Panel had noted the definitions of the terms used by Archer *et al* and considered that the term 'no bleeding' was effectively amenorrhoea. The Panel had noted that the original abstract of the Archer paper used the term amenorrhoea to define a state of no spotting or bleeding. The Panel had considered that use of the term amenorrhoea could thus be justified and was thus not misleading as alleged. No breach of the Code had been ruled.

Turning to the present case, Case AUTH/1417/2/03, the Panel noted that Wyeth made reference to Johnson *et al* (2002) wherein the incidence of no bleeding and no spotting for Kliovance cycles 1-3 was 58.5%.

The Panel noted that the figure of 73% had not been at issue in Case AUTH/1235/10/01 which had considered whether amenorrhoea was an appropriate term to describe the Kliovance data referenced to Archer *et al* (1999). The Panel noted that in the present case Wyeth similarly queried the use of the term amenorrhoea to describe the Kliovance data from Archer *et al* and on this narrow point considered that its ruling in Case AUTH/1235/10/01 was relevant and ruled no breach of Clause 7.2 of the Code.

In relation to the allegation that 73% was not a fair reflection of the evidence the Panel noted that the figure of 58.5% for the percentage of patients who experienced no bleeding and no spotting during Kliovance cycles 1-3 in Johnson *et al* was markedly different to that depicted in the bar chart. The Panel noted that the data in the leavepiece at issue depicted the incidence of amenorrhoea and considered that given Johnson *et al* it was no longer a fair reflection of the balance of the evidence on this point. A breach of Clause 7.2 was ruled. This ruling was appealed.

APPEAL BY NOVO NORDISK

Novo Nordisk noted that Archer *et al* had reported a double-blind, randomised, 4-arm parallel group study involving 1,176 women at least 12 months post menopause, of whom 295 were on Kliovance, examining bleeding profiles over a 12 month period. The other three comparator arms were unopposed oestradiol 1mg; oestradiol 1mg plus norethisterone acetate 0.1mg and oestradiol 1mg plus norethisterone acetate 0.25mg. The aim was to look at the effect of the progestogen norethisterone on the bleeding profile. Johnson *et al* described a double-blind, randomised 2-arm parallel group study involving 438 women at least 12 months post menopause and compared bleeding profiles over a 6 month period between Kliovance (n=217) and Prempro (n=221) (0.625mg conjugated equine estrogens and 2.5mg of medroxyprogesterone acetate).

Novo Nordisk noted that crucially Johnson *et al* had reported 2 cumulative amenorrhoea rates for 1-3 and 4-6 months whereas Archer *et al* reported point incidence percentages of women who had amenorrhoea at months 2, 5, 8 and 11. In effect two entirely different comparisons were being made – a point incidence at 2 months and a cumulative (additive) incidence for 3 separate months, including all the women who bled in the first month and not in the second etc. Data obtained from Johnson *et al* for each month separately showed that the figure for women less than 3 years from the menopause with amenorrhoea (no bleeding or spotting) at month 2 was 73%, the same figure as the Archer paper. The Kliovance SPC stated that it should be started 12 months after the menopause. In the UK most women were started on continuous combined HRT less than 3 years after the menopause, unlike in the USA.

Novo Nordisk submitted that further evidence from other published papers and data on file, not only supported its claim but suggested that this might be the lower limit for amenorrhoea and not the upper limit as originally implied by Wyeth.

Von Holst *et al* (2002) reported a point incidence figure of 86.3% of women having no irregular bleeding (defined as no spotting or irregular bleeding) at 3 months in the group of women more than 12 months after the menopause. This study had examined 446 late peri- and postmenopausal women in a randomised, open-label, 2-arm parallel group design. The comparison here was the continuous combined therapy Kliovance against a sequential regimen of 0.625mg conjugated equine estrogens for 28 days with 5mg medrogestone for the final 14 days of the cycle. The study duration was 9 months. The unpublished study report recorded an incidence of amenorrhoea of 80.8% at 2 months, higher than 73% figure in question.

Stadberg *et al* (1996) had reported a pilot study comparing Kliovance with Kliofem (oestradiol 2mg, norethisterone acetate 1mg) and oestradiol 1mg + norethisterone acetate 0.25mg in 60 postmenopausal women. This was a double-blind, randomised, single centre, 3 arm, parallel group design over 1 year and from a graph presented in the published paper suggested an amenorrhoea rate of approximately 75% for Kliovance.

Novo Nordisk submitted that it was clear that Johnson *et al* supported the figure of 73% amenorrhoea at 2 months since this was exactly the figure in the study report for women who were less than 3 years since the menopause; von Holst *et al* further suggested the true figure for amenorrhoea at 2 months may be higher than 73%.

COMMENTS FROM WYETH

Wyeth noted that Novo Nordisk had provided one page of the 95-page unpublished Johnson *et al* study report. In the table of data on that page the per cycle amenorrhoea rate for month 2 was 73% for patients within 3 years of menopause. However, for patients 3 or more years since menopause the amenorrhoea rate at month 2 was 70%. In the published Johnson *et al* paper it had stated 'Summary of bleeding and spotting (**all subjects**)' (emphasis added). It was therefore clearly unacceptable for Novo Nordisk to select a subgroup of patients in the study report for whom the amenorrhoea rate was higher, namely 'women less than 3 years from the menopause'. Although Novo Nordisk had not provided data for the overall amenorrhoea rates for all patients at month 2, it was clear that this fell between 70% and 73%, and would certainly be less than 73%.

Wyeth noted that it had not seen the full unpublished Johnson *et al* study report data referred to by Novo Nordisk. Wyeth stated that if this was provided, it could fully respond to the appeal and so requested sight of the full study report data. Wyeth would specifically like to see data confirming what the overall amenorrhoea rates were for all subjects.

Wyeth alleged that despite Novo Nordisk failing to submit all pertinent data, it considered adequate data had been submitted to enable a decision to be made, and it would request that the Appeal Board considered ruling a breach of the Code on the point of use of the 73% amenorrhoea rate at month 2.

APPEAL BOARD RULING

The Appeal Board noted that Archer *et al* had reported that 73% of women were amenorrhoeic on Kliovance at month 2 of treatment. Von Holst *et al* had reported that 86.3% of women on Kliovance had no irregular bleeding at 3 months and a figure of 75% of women reporting amenorrhoea at 2 months on Kliovance could be approximated from a graph in Stadberg *et al*.

The Appeal Board noted Novo Nordisk's comments about the misunderstanding of the Johnson *et al* study. The published data referred to a cumulative incidence for 3 separate months (58.5%) and not a point incidence (73%) as in Archer *et al*. The Appeal Board noted that a retrospective analysis of the unpublished data from Johnson *et al* had shown that in women less than three years from the menopause, 73% had reported amenorrhoea at month 2 on Kliovance; in women more than three years since the menopause the comparable figure was 70%. Further retrospective analysis from the unpublished von Holst *et al* data had shown that 80.8% of women were amenorrhoeic at month 2 on Kliovance although this figure was disputed by Wyeth at the appeal as it considered that it represented per protocol data as opposed to intent to treat data. Wyeth contended that the figure for intent to treat at month 2 would be lower; this point was accepted by Novo Nordisk.

The Appeal Board queried the validity of retrospective analyses of unpublished data. The Appeal Board considered that 73% of women reporting amenorrhoea at month 2 on Kliovance was a fair reflection of the available published evidence. Archer *et al* was a large trial, 295 women were in the Kliovance group. The other studies cited by Novo Nordisk had not published directly comparable data although the unpublished data from these studies was not inconsistent with Archer *et al*. The Appeal Board ruled no breach of Clause 7.2. The appeal on this point was successful.

Complaint received **14 February 2003**

Case completed **24 July 2003**

PFIZER v LILLY

Brochure and material on UK website

Pfizer complained about a brochure entitled 'ManMatters Information and Advice on Erection Problems' and material on a website sponsored by Lilly. The brochure could be downloaded from the Internet without a password, requested by post (via a freephone telephone number) and was advertised in the national newspapers and through GP surgeries and certain pharmacies.

Pfizer noted that the oral treatments section of the brochure described treatments which might need to be taken just before (20 minutes to one hour) or any time up to 12 hours before sexual activity. Pfizer stated that there was only one treatment available [Lilly's product, Cialis] claiming to fulfil the second criterion and it therefore alleged that the ManMatters brochure advertised a prescription only medicine directly to the public. Questions for a patient to ask his doctor, particularly those related to speed of onset of action and longevity of effect, appeared to lead the reader to only one possible conclusion.

Pfizer noted the closing paragraph 'Even if you've received treatment in the past, it is important to talk to your doctor/nurse again since newer treatments are increasingly available and they will be able to suggest one that's right for you'. Pfizer was not aware of any new treatments available other than Cialis (Lilly's materials were available prior to the marketing authorization for Levitra). Pfizer alleged that this statement was promotional.

Pfizer's product was Viagra (sildenafil).

The Panel considered that the discussion of the type of treatments available was biased towards oral therapy; most of one page was given over to a discussion of oral treatments with other treatments discussed in just two or three lines each on another page. The Panel considered that the brochure would encourage patients to ask their doctors for an oral therapy. There were, nonetheless, a number of oral treatments available for the treatment of erectile dysfunction and the brochure did not promote directly or indirectly a specific oral medicine. In the Panel's view the brochure did not constitute advertising a prescription only medicine to the general public as alleged. No breach of the Code was ruled.

Pfizer noted that the following information was also available without a password on a Lilly Icos sponsored website:

'Cialis can be taken from 30 minutes to 12 hours prior to intercourse. It can be taken with or without food.

Viagra should be taken about one hour before intercourse. It works better when taken on an empty stomach, as this increases its absorption into the bloodstream.'

Then by clicking on Cialis the following information became available:

'As tadalafil enhances the actions of the chemical messengers responsible for producing an erection, it will only work once these messengers are present. This means that sexual stimulation is required for it to produce and maintain an erection. *The dose can be taken from 30 minutes to 12 hours before intended intercourse, and it may produce an erection in response to sexual stimulation up to 24 hours after taking the dose*' [emphasis added].

Then by clicking on Viagra the comparable information appeared:

'As sildenafil enhances the actions of the chemical messengers responsible for producing an erection, it will only work once these messengers are present. This means that sexual stimulation is required for it to produce and maintain an erection. *The dose should be taken approximately one hour before intended intercourse*' [emphasis added].

Pfizer questioned making this information available to the public. The way in which it had been selected and presented had turned this information into advertising a prescription only medicine to the public. Pfizer alleged a breach of the Code.

The Panel noted that it was clearly stated that the ED section of the website was sponsored by Lilly Icos. The Panel noted from Lilly's submission that it had provided an educational grant to assist in the development of an improved updated erectile dysfunction section of NetDoctor. The Panel also noted that Lilly had no editorial input into the copy on the website other than the ManMatters brochure. Lilly had provided a summary of product characteristics (SPC) and had reviewed the wording for factual inaccuracies only.

The Panel noted that NetDoctor stated that it maintained strict control over its content and did not allow sponsors to edit or direct what was printed. The Panel noted that the ManMatters brochure featured a website address on its front page which led readers directly to the homepage of netdoctor.co.uk from where a banner advertised the ManMatters brochure. Lilly had no editorial control over the site but it was referring people to the site. Therefore the matter was covered by the Code.

The Panel did not consider that the material highlighted by Pfizer in its complaint was unreasonable. It was based on comparable information in the respective SPCs and patient information leaflets. The section referred to all medicines to treat erectile dysfunction. None was given prominence.

The Panel did not consider that the website advertised prescription only medicines to the public as alleged by Pfizer and no breach of the Code was ruled.

Pfizer was concerned about the following questioning and answer:

Question 'I thought Viagra would be the answer for me, but my doctor won't give it to me because I'm on drugs for my heart. He says I should try injections, but I've never liked the thought of

needles much, and the thought is enough to put me off sex for life. Is there an alternative?'

Answer 'It's true that certain heart drugs are highly dangerous in combination with Viagra. Other treatments include: 1 Psychotherapy; 2 Anti-impotence pellets, which you put into the penis; 3 Injections-though you're not keen on them; and 4 Vacuum cylinders.

Other drugs will be along soon. Good luck.'

Signed [named] GP.

Whilst Pfizer acknowledged that Viagra was contraindicated with nitrates it considered the choice of language 'highly dangerous' to be inappropriate. Pfizer was also aware that both Levitra and Cialis which had been launched recently carried a similar warning and it therefore considered that the answer provided above was misleading the reader to the fact that either of the new products, which like Viagra were phosphodiesterase-5 (PDE5) inhibitors, could overcome Viagra's limitations with regards to contraindications.

The Panel noted its comments about the position of the website in relation to the Code. The Panel was concerned about the use of the phrase 'highly dangerous' but did not consider that the answer provided misled readers into thinking that either Levitra or Cialis could overcome Viagra's limitations with regard to contraindications as alleged. No mention was made of PDE5 inhibitors only that 'Other drugs will be along soon'. The Panel ruled no breach of the Code.

Pfizer alleged that Lilly's behaviour brought the industry into disrepute.

The Panel noted its rulings above. The Panel did not consider that the materials at issue warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Pfizer Limited complained about a brochure entitled 'ManMatters Information and Advice on Erection Problems' and material on a website sponsored by Eli Lilly and Company Limited.

1 ManMatters brochure sponsored by Lilly Icos

Lilly stated that a brochure entitled ManMatters could be downloaded from the Internet having been posted on a public access website on 10 March 2003. The printed brochure was also available from 10 March 2003. The brochure could be requested by post (via a freephone telephone number). It was also advertised in the national newspapers, via a GP waiting room campaign and via certain pharmacies. Pfizer stated that the brochure was also available on the Internet without a password.

COMPLAINT

Pfizer noted that the oral treatments section of the brochure described treatments which might need to be taken just before sexual activity (20 minutes to one hour) or any time up to 12 hours before sexual activity. To the best of Pfizer's knowledge, there was only one treatment available [Lilly's product, Cialis] claiming to fulfil the second criterion and it therefore alleged that the ManMatters brochure advertised a prescription only medicine directly to the public in breach of Clause 20.1 of the Code.

Pfizer stated that the list of questions for a patient to ask his doctor in the section 'How should I discuss treatment options?', particularly the questions which related to the speed of onset of treatments and the longevity of effect, appeared to be leading the reader to only one possible conclusion.

Pfizer highlighted the closing paragraph 'Even if you've received treatment in the past, it is important to talk to your doctor/nurse again since newer treatments are increasingly available and they will be able to suggest one that's right for you'. Pfizer was not aware of any new treatments available other than Cialis (these materials were available prior to the marketing authorization for Levitra). Pfizer alleged that this statement was promotional.

Pfizer's product was Viagra (sildenafil).

RESPONSE

Lilly stated that the website NetDoctor.co.uk on which the brochure appeared was not owned by Lilly and existed as a public access medical information website long before Lilly provided sponsorship. Prior to Lilly's sponsorship NetDoctor already had a section on impotence which discussed the treatment options available. There were also treatment fact sheets on the site for all of the treatments available for erectile dysfunction (ED) at the time. Lilly's educational grant merely assisted in the development of an improved, updated ED community as part of NetDoctor, similar to existing communities on NetDoctor for depression and smoking.

Apart from the ManMatters brochure on the ED community, the content of the site was independently developed by NetDoctor and Lilly had no editorial input into the copy posted on the web as part of the ED community, much of which predated Lilly's sponsorship. Lilly provided NetDoctor with a copy of the Cialis summary of product characteristics (SPC) which was a publicly available document providing factual information. Lilly reviewed the wording relating to Cialis for factual inaccuracies only. Confirmation that Lilly was not in control of the content of this site other than in relation to the ManMatters brochure was set out in a letter from NetDoctor.

Lilly stated that Pfizer was incorrect in its assertion that only one entirely new agent was available at the time the brochure was made available to the public on NetDoctor.co.uk. The website posted ManMatters on 10 March whereas the Levitra marketing authorization was dated 7 March. Thus at least two entirely new treatments were available at the time ManMatters was posted on the Internet.

Lilly considered that Pfizer took too narrow a view of what might be a new treatment to a particular patient. Pfizer overlooked the possibility that many patients would not have raised their ED problems with their doctors for some years in which case, depending on the date of the last consultation, any number of

treatments for ED would be 'new' for those patients. It was even possible that Pfizer's Viagra would be a 'new' product for consideration in some cases. Lilly provided a list of ED treatments available since 1997. Thus, suggesting that there may be new treatments did not point only to the existence of one product and as such did not constitute marketing a prescription only medicine to the general public.

ED Products first licensed/marketed since 1997

Year	*Product (brand name)*	*Route of administration*
1997	Viridal duo	Parenteral
1998	Muse	Trans-Urethral
	Viagra	Oral
2000	Caverject	Parenteral
2001	Uprima	Oral
2002	Raport	Mechanical device
	Elite	Mechanical device
	Ericaid	Mechanical device
	Cialis	Oral
2003	Levitra	Oral

(NB products all listed in MIMS 3/03)

Lilly submitted that the questions suggested to assist the patient in consulting his GP were very pertinent; they were relevant to all of the products on the market and which product would be 'better' depended on the patient's particular situation. There was certainly not just one conclusion that could result from the questions. Not all patients wanted the same things. Speed of onset and duration of treatment were entirely a matter of personal taste in sexual matters. With some ED treatments a very rapid response was available ensuring that the patient knew for sure if he was going to be able to perform (eg injection treatments). With some ED treatments the effect might persist for as long as the patient wished, allowing the patient to be confident of the reliability of the treatment effect (eg mechanical devices such as penile rings). With some other treatments the dosing interval allowed the possibility of a response (in the presence of sexual stimulation) for some hours after the drug was taken, but here patients might also be concerned about how long any side effect of treatment, such as visual disturbances, might persist. Obviously if these issues were important to a patient they needed to be raised with the doctor and might direct treatment in any number of directions. Thus Pfizer's allegation that the suggested questions also directed the patient to ask for only one possible treatment was unfounded.

Finally, Lilly refuted the suggestion that there were any specific references in the piece which could constitute advertising a prescription only medicine to the public, indeed Lilly took the view that the Code only applied to these materials in the sense that it defined them as being non-promotional and thus outside the scope of the rest of the Code. The reason for this was that they were statements relating to human health or disease and there was no reference direct or indirect to specific medicines (Clause 1.2). The fact that it was sponsored by Lilly and was posted on a UK website did not on its own bring it within the scope of all clauses of the Code. It would be noted that no brand or generic name of any medicine was mentioned in ManMatters, that the two pages on available treatments referred generally to the broad range of treatments available and not to specific treatments. In addition the pages provided factual, balanced, fair and objective information.

The section on oral treatments did not distinguish any specific oral treatment. It discussed the oral treatments generally and where relevant provided the ranges within which certain characteristics of the products came rather than specifying each product individually. It presented the overall picture. For instance, the reference to up to 12 hours to which Pfizer referred showed the range that was available across the treatments. The pharmacodynamic half-life of Viagra fell at about the mid point of the range cited and the proposition complained of had two parts not one as implied by Pfizer. Time issues had obvious practical implications which needed to be discussed between the patient and the doctor along with other issues which might determine the most appropriate treatment (was the patient taking nitrates for any reason?, did the patient have trouble swallowing?). The section covered a range of issues relevant to the choice of treatment. The section also made it clear that this information was 'for example' and that there might be other information that needed to be considered in relation to a particular patient. Hence, it was not clear from this information that the patient should go and ask their doctor for only one of the products available. Furthermore, clear guidance was given encouraging the patient to talk to his doctor about treatments on several occasions in the section.

For all these reasons the brochure did not encourage a patient to go and see a doctor and ask for a specific medicine. It encouraged a patient to talk to the doctor about his ED problem and seek treatment for it. The brochure helped people talk to their doctor in an informed way about a difficult, and for some, very embarrassing issue. Hopefully this resulted in better information being provided to the doctor about their problem and hence what treatment would best suit the patient. This should then result in the best possible outcome for the patient. In summary the brochure did not advertise a prescription only medicine to the general public.

Finally, Lilly noted Pfizer's allegations about the possible meaning of the section about oral treatments, which described treatments, which might need to be taken just before sexual activity (20 minutes to one hour) or any time up to 12 hours before sexual activity. Contrary to Pfizer's reading, the section on oral treatments did not distinguish any specific oral treatment. It discussed the oral treatments generally and where relevant provided the ranges within which certain characteristics of the products came rather than specifying each product individually. It presented the overall picture. In summary the information in the brochure did not result in the disguised promotion of a specific prescription only medicine to the general public.

PANEL RULING

The Panel considered that patient education programmes were a legitimate activity for a

pharmaceutical company to undertake provided that such programmes were in accordance with the Code. Such activities might facilitate the market development of the sponsoring company's products but this was not necessarily in breach of the Code. Each case would need to be judged on its merits.

The Panel noted that the definition of promotion given in Clause 1.2 of the Code excluded statements relating to human health or disease provided there was no reference, either direct or indirect, to specific medicines. Clause 20.1 prohibited the advertising of prescription only medicines to the general public. Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

The twelve page brochure in question was entitled 'Information and advice on erection problems' and the front page stated that www.manmatters.netdoctor.co.uk was sponsored by Lilly lcos and the Lilly / Icos and netdoctor logos were included. The website address, www.manmatters.netdoctor.co.uk led the reader directly to the homepage of netdoctor.co.uk in the top right-hand corner of which was a banner, described as an advertisement, from which one could download a copy of the brochure or request it via a telephone helpline.

The booklet described erection problems and their causes. Treatments were referred to on pages 6 and 7. The opening paragraph stated for further information about treatments talk to your doctor and '… even if you had tried treatments in the past, since newer ones are increasingly available'. The next section, which occupied most of page 6, discussed oral treatments. The section stated that oral treatments varied in the way that they worked and depending on which one was received it might need to be taken just before sexual activity or any time up to 12 hours before sexual activity. Reference was made to the fact that the time period over which different treatments worked could vary from between 3 hours and up to 24 hours.

The following page mentioned other treatments. Details were given about alprostadil, vacuum pumps, hormone treatment, surgery and counselling. It was also stated that a range of products such as herbal remedies were available over the Internet.

The Panel did not consider that the brochure met the exemption to the definition of promotion for statements relating to human health or diseases provided there was no reference either direct or indirect to specific medicines.

The Panel considered that the discussion of the type of treatments available was biased towards oral therapy. Most of page 6 was given over to a discussion of oral treatments whereas other treatments available were all discussed, in just two or three lines each, on page 7. The Panel considered that the brochure would encourage patients to ask their doctors for an oral therapy. There were, nonetheless, a number of oral treatments available for the treatment of ED and the brochure did not promote directly or indirectly a specific oral medicine. In the Panel's view the brochure did not constitute advertising a prescription only medicine to the general public as alleged. No breach of Clause 20.1 of the Code was ruled.

2 Medicines to treat ED section on NetDoctor.co.uk

COMPLAINT

Pfizer noted that the following information was also available without a password from the NetDoctor site:

'**Cialis** can be taken from 30 minutes to 12 hours prior to intercourse. It can be taken with or without food.

Viagra should be taken about one hour before intercourse. It works better when taken on an empty stomach, as this increases its absorption into the bloodstream.'

By clicking on Cialis the following information became available:

'As tadalafil enhances the actions of the chemical messengers responsible for producing an erection, it will only work once these messengers are present. This means that sexual stimulation is required for it to produce and maintain an erection. *The dose can be taken from 30 minutes to 12 hours before intended intercourse, and it may produce an erection in response to sexual stimulation up to 24 hours after taking the dose*' [emphasis added].

Then by clicking on Viagra and the paragraph placed in the context of the document similarly to the above appeared:

'As sildenafil enhances the actions of the chemical messengers responsible for producing an erection, it will only work once these messengers are present. This means that sexual stimulation is required for it to produce and maintain an erection. *The dose should be taken approximately one hour before intended intercourse*' [emphasis added].

Pfizer questioned making this information available to the public. More importantly, however, what information had been selected (Pfizer presumed by the sponsors Lilly Icos) and how it was presented, in Pfizer's view turned this 'provision of information' into advertising a prescription only medicine to the public. Pfizer alleged a breach of Clause 20.1 of the Code.

RESPONSE

As discussed above Lilly had no editorial control over the part of the website at issue and could not therefore be held responsible for its content under the Code. Not withstanding this, Lilly's comments on Pfizer's complaint were as follows:

Pfizer had highlighted two small sections of text taken from standard formats based on the SPCs and patient information leaflets (PILs) for the medicines. These were documents available in the public domain.

Pfizer had not commented on the fact that all seven medicines available in the UK for the treatment of ED were described in an identical manner using an identical format in language similar to that found in the PILs for those products. The text was presented in a balanced, neutral, factual manner and was non-promotional.

Lilly denied a breach of Clause 20.1 of the Code: much of the information was posted on NetDcotor.co.uk before Lilly's involvement as a sponsor, the information was presented in a balanced, neutral, factual manner as required by the Code, was based on documents in the public domain (SPCs, PILs) similar to the patient information section of the Electronic Medicines Compendium.

PANEL RULING

The Panel noted that the ED section of NetDoctor had been sponsored jointly by Lilly Icos. In relation to published material Clause 9.9 (2001 edition) required material relating to medicines to so declare if it had been sponsored by a pharmaceutical company even if the material was non-promotional. The Panel noted that it was clearly stated that the ED section of the website was sponsored by Lilly Icos.

The Panel noted that it was acceptable for companies to sponsor material. It had previously been decided that the content would be subject to the Code if it was promotional in nature or if the company had used the material for a promotional purpose. Even if neither of these applied, the company would be liable if it had been able to influence the content of the material in a manner favourable to its own interests. It was possible for a company to sponsor material which mentioned its own products and not be liable under the Code for its contents, but only if it had been a strictly arm's length arrangement with no input by the company and no use by the company of the material for promotional purposes. The Panel noted from Lilly's submission that it had provided an educational grant to assist in the development of an improved updated ED community as part of NetDoctor. Prior to Lilly's sponsorship NetDoctor already had a section on impotence and treatment options. There were also treatment fact sheets on the site for all of the treatments available at the time. The Panel also noted that Lilly had no editorial input into the copy on the website other than the ManMatters brochure. Lilly had provided an SPC and had reviewed the wording for factual inaccuracies only.

The Panel noted that NetDoctor stated that it maintained strict control over its content and did not allow sponsors to edit or direct what was printed. Information about medicines was based only on recognised reference standard documentation including SPCs. NetDoctor stated that it presented information on all available treatment options and offered no preference or recommendation in favour of one over another.

The Panel noted that the ManMatters brochure featured the website address www.manmatters.netdoctor.co.uk on its front page. This led readers directly to the homepage of netdoctor.co.uk from where a banner advertised the ManMatters brochure. Lilly had no editorial control over the site but it was referring people to the site. Therefore the matter was covered by the Code.

The Panel did not consider that the material highlighted by Pfizer in its complaint was unreasonable. It was based on comparable information in the respective SPCs and PILs. The section referred to all medicines to treat ED. None was given prominence.

The Panel did not consider that the website advertised prescription only medicines to the public as alleged by Pfizer and no breach of Clause 20.1 of the Code was ruled.

During its consideration of this case the Panel was concerned that in the section headed 'How long do they take to work?' the description of Cialis referred to the fact that the effects of Cialis lasted for up to 24 hours and stated that 'This may provide an advantage to couples because the man won't have to take a tablet just before sex, and this could make sex more spontaneous'. The Panel considered that this might encourage patients to ask their doctors to prescribe Cialis. It thus queried whether the materials met the requirements of Clause 20.2 of the Code. The Panel requested that Lilly be advised of its concerns. Lilly should also be advised to review the rest of the site for compliance with the Code given that as it was sponsoring the site, had reviewed the text for factual inaccuracies and was actively referring people to it, it was liable under the Code for its content.

3 Ask the doctor section on NetDoctor.co.uk

COMPLAINT

Pfizer was concerned about the following questioning and answer which was available from the NetDoctor site without a password:

Question

'I thought Viagra would be the answer for me, but my doctor won't give it to me because I'm on drugs for my heart. He says I should try injections, but I've never liked the thought of needles much, and the thought is enough to put me off sex for life. Is there an alternative?'

Answer

'It's true that certain heart drugs are highly dangerous in combination with Viagra. Other treatments include:

1. Psychotherapy
2. Anti-impotence pellets, which you put into the penis
3. Injections-though you're not keen on them
4. Vacuum cylinders

Other drugs will be along soon. Good luck'.

Signed [named] GP.

Whilst Pfizer acknowledged that Viagra was contraindicated with nitrates it considered the choice of language 'highly dangerous' to be inappropriate. Pfizer was also aware that both Levitra and Cialis which had been launched recently, carried a similar

warning and it therefore believed that the answer provided above was misleading the reader to the fact that either of the new products, which like Viagra were phosphodiesterase-5 (PDE5) inhibitors, could overcome Viagra's limitations with regards to contraindications. Pfizer therefore alleged a breach of Clause 7.2.

RESPONSE

Lilly stated that it had no editorial control over the part of the website in question and in any event, Lilly submitted that the GP's contribution was acceptable for the following reasons:

Lilly was surprised at Pfizer's PDE5-centric interpretation of the initial question asked by the patient; he was asking for alternative treatments not for alternative PDE5 inhibitors. Thus the reply was not misleading because it did not suggest that other PDE5 inhibitors were devoid of the cardiac safety concerns which surrounded Viagra. In this context Lilly was also surprised about Pfizer's contention that the combination of Viagra with nitrates was not 'highly dangerous'; there were numerous case reports of fatalities attributable to this very combination eg Kloner *et al* (1999) reported that the FDA had received 77 reports of cardiovascular deaths associated with the use of Viagra in the first 6 months of marketing, of which 19 were in patients taking nitrates.

Lilly was surprised at Pfizer's PDE5-centric interpretation of the suggestion that 'other drugs will be along soon'. The named GP did not mention either of the available alternative PDE5 inhibitors but expressed a hope that other [as yet un-marketed] new medicines would eventually solve the patient's problem.

PANEL RULING

The Panel noted its comments about the position of the website in relation to the Code in point 2 above.

The Panel was concerned about the use of the phrase 'highly dangerous' but did not consider that the answer provided misled readers into thinking that either Levitra or Cialis could overcome Viagra's limitations with regard to contraindications as alleged. No mention was made of PDE5 inhibitors only that 'Other drugs will be along soon'. The Panel ruled no breach of Clause 7.2 of the Code.

4 Alleged breach of Clause 2

COMPLAINT

Pfizer stated that given Lilly's past history on Cialis promotion and the fact of having been severely cautioned on it in the past, it would have expected greater care on Lilly's behalf where Cialis promotion was concerned. Pfizer alleged that Lilly's behaviour brought the industry into disrepute in breach of Clause 2 of the Code.

RESPONSE

Lilly was disappointed to learn that Pfizer considered the provision of neutral, objective, fair and balanced information about human health and disease to the general public via a reputable website constituted not just a breach of the Code, but one so severe as to bring the industry into disrepute. Lilly took the view that the provision of the information which it had sponsored had not brought the pharmaceutical industry into disrepute but had enhanced its reputation for providing a range of useful treatment options for improving human health and treating disease. This was a view which the ABPI itself actively promoted in a number of other therapeutic areas. Thus Lilly believed that its activities in the context of NetDoctor.co.uk were not in breach of Clause 2 of the Code.

PANEL RULING

The Panel noted its rulings above. The Panel did not consider that the materials at issue warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Complaint received **31 March 2003**

Case completed **18 July 2003**

CASE AUTH/1459/4/03

BAYER v WYETH

Tazocin booklet

Bayer complained about a booklet for Tazocin (piperacillin/tazobactam) issued by Wyeth which was aimed at hospital doctors, including microbiologists, intensivists, oncologists, immunologists and those particularly familiar with antibiotic use. Bayer supplied Ciproxin (ciprofloxacin).

Bayer alleged that the heading 'A confident choice in nosocomial pneumonia' implied that Tazocin had been used in all patients with chest infections, whereas the reference cited, Wade *et al* (2000), was in a select group of subjects following liver transplantation. It was possible to deduce this fact only by carefully searching the page for the ** legend which was placed at the bottom of the page, beneath a separate bar chart relating to a different study. The presentation of the bar chart beneath the heading exaggerated the role of Tazocin and disparaged Bayer's product ciprofloxacin. The differences between the outcome of the regimens compared were not statistically significant, but unlike the subsequent bar chart on the same page neither bar chart was labelled as non-significant. This was misleading.

The Panel noted that Wade *et al* compared Tazocin with ciprofloxacin plus amoxycillin for infective episodes in patients after orthotopic liver transplantation and concluded that empirical monotherapy with Tazocin was clinically highly efficacious and just as effective as ciprofloxacin plus amoxycillin.

The Panel considered that the bar chart at issue gave the impression that the data depicted applied to all patients with hospital-acquired lower respiratory tract infection which was not so. The Panel considered that by not clearly stating that the specific results shown related to liver transplant patients, the bar chart was misleading; readers were unable to judge the clinical significance of the data shown. A breach of the Code was ruled. The Panel did not consider the page exaggerated on this narrow point and no breach was ruled. Upon appeal by Wyeth, the Appeal Board noted that only one ciprofloxacin combination had been compared with Tazocin, whereas the subheading to the page 'Tazocin monotherapy compares favourably with ciprofloxacin combination' implied otherwise. The Appeal Board upheld the Panel's ruling of a breach of the Code.

The Panel noted that Wade *et al* concluded that Tazocin was just as effective as ciprofloxacin and amoxycillin. The Panel noted that the p values were stated in small print above each bar chart at 72 hours and end of the study. The Panel considered that the longer length bars depicted for Tazocin in the bar chart and the prominent greater percentage clinical response stated on each Tazocin bar than each ciprofloxacin bar gave the immediate visual impression that the difference between the products was statistically significant in favour of Tazocin and that was not so. This impression was compounded by the heading 'A confident choice in nosocomial pneumonia' and the sub-heading 'Tazocin monotherapy compares *favourably* with ciprofloxacin combination therapy in chest infections' (emphasis added). The presence of the non-significant p values was insufficient to negate the overall visual impression. The Panel considered that the presentation of the data was misleading and exaggerated the differences between the products; breaches of the Code were ruled. Upon appeal by Wyeth, the Appeal Board upheld the Panel's rulings.

The Panel noted that in the first bar chart non-significant p values were stated with their numerical value; the second bar chart used the term p=ns to indicate non-significance. The Panel considered that although the abbreviations used were inconsistent they were not misleading and in that regard ruled no breach of the Code.

The emboldened claims 'Unlike ciprofloxacin, Tazocin can be administered by bolus injection as well as infusion' and 'Tazocin has a low propensity to cause superinfection:' appeared on a page headed 'Tazocin is well tolerated in clinical practice …'. The latter claim was followed by 3 bullet points, the third of which read '-Less likely to lead to MRSA than ciprofloxacin or cephalosporins' referenced to Smith (1999).

Bayer stated that claims were made regarding the tolerability of Tazocin in clinical practice whereas the claim 'Unlike ciprofloxacin, Tazocin can be administered by bolus injection as well as infusion' had nothing to do with tolerability and was intended to cause doubt in the mind of clinicians regarding ciprofloxacin. The claim was exaggerated and intended to discredit ciprofloxacin.

Smith referred to changes in antibiotic use in community medical centers in the USA and indicated that a decrease in resistance between 1994 and 1998 was 'attributable to a cohesive working relationship between pharmacists, microbiologists and infectious diseases physicians and personnel and a decision to decrease administration of cephalosporins in favour of piperacillin-tazobactam'. The purpose of the programme was 'to determine if reductions in administration of cephalosporin, imipenem and vancomycin could favorably affect gram-negative resistance'. In the results section the author indicated that 'ciprofloxacin and ampicillin-sulbactam use remained relatively constant'. The only mention of ciprofloxacin and MRSA was in the discussion, where Hill *et al* (1998) was quoted as stating 'One report stated that either ciprofloxacin or a cephalosporin was significantly associated with acquisition of MRSA'. Hill *et al*, a letter to a journal, indicated the uncorroborated results of a 'small pilot study' which suggested that limiting the use of cephalosporins and ciprofloxacin was one means of minimising selection and dissemination of MRSA. Whilst indicating that administration of ciprofloxacin or a cephalosporin was significantly associated with acquisition of MRSA, the authors also stated 'It is not clear why some antibiotics to

which MRSA strains are resistant influence colonization more than others'. Neither this reference, nor the one cited within the text of the page, supported the contention that Tazocin was less likely to lead to MRSA than the two antibiotics mentioned. Bayer alleged that by oversimplification of a very complex topic of antibiotic resistance in an attempt to denigrate ciprofloxacin, Wyeth had failed to present a full and balanced account of the resistance issue.

The Panel considered that the emboldened claim 'Unlike ciprofloxacin, Tazocin can be administered by bolus injection as well as infusion' which appeared on a page which discussed tolerability, implied that ciprofloxacin was generally less well tolerated than Tazocin due to its mode of administration. The claims were referenced to the respective products' summaries of product characteristics (SPCs), neither of which discussed mode of administration in relation to tolerability. The Panel considered that in the context in which it was used the claim was misleading. A breach of the Code was ruled. Upon appeal by Wyeth, the Appeal Board upheld the Panel's rulings.

The Panel noted that the booklet was aimed at hospital doctors who would be very familiar with the issues of antibiotic use and resistance, particularly MRSA. There was data suggesting a link between ciprofloxacin and MRSA. The claim at issue, however, suggested that the risks of MRSA emerging with Tazocin therapy and those associated with ciprofloxacin therapy were known and that there was a significant difference, in favour of Tazocin, between the two. This was not so. The Panel considered that the claim 'Less likely to lead to MRSA than ciprofloxacin and cephalosporins' overstated that data and was misleading in that regard. Breaches of the Code were ruled. Upon appeal by Wyeth, the Appeal Board upheld the Panel's rulings.

The Panel considered that the section headed 'Tazocin has a low propensity to cause superinfection' oversimplified the issue of superinfection. It was not a fair reflection of the data and was exaggerated in this regard; a breach of the Code was ruled. Upon appeal by Wyeth, the Appeal Board noted that the heading implied an absolute rather than a relatively low likelihood to lead to MRSA and yet there was no data to support such an implication. In addition, ciprofloxacin was widely used in the community whereas Taxocin was not. Pre-exposure in the community might be a factor in the potential to develop MRSA in hospital. The Appeal Board upheld the Panel's ruling of a breach.

Bayer alleged that the claim 'The incidence of MRSA is growing, with the usage of fluoroquinolones in humans and animals fuelling the problem of resistance', referenced to Hooper (2001) and McKellar (2001), was exaggerated and all-embracing. The resistance issue was multifactorial and could not be simplified to a single headline. Bayer further alleged that Wyeth had thus indirectly disparaged ciprofloxacin.

The Panel noted its comments above in relation to the claim 'Less likely to lead to MRSA than ciprofloxacin or cephalosporins'. The Panel considered that the claim 'The incidence of MRSA is growing, with the use of fluoroquinolones in humans and animals fuelling the problem of resistance' gave the impression that use of fluoroquinolones in humans and animals was the main driver and that was not necessarily so. There was some evidence regarding the use of fluoroquinolones in animals and the possible transfer of resistant organisms to humans but not MRSA *per se*. The emergence of MRSA in humans was multifactorial. The claim overstated the data and was thus misleading and exaggerated the role of fluoroquinolones, including ciprofloxacin as alleged. Breaches of the Code were ruled. Upon appeal by Wyeth, the Appeal Board upheld the Panel's rulings.

Bayer stated that the claim 'Limiting the use of cephalosporins and ciprofloxacin is one means of minimising the selection and dissemination of MRSA' was a repetition of the all-embracing claim about limitation of use of ciprofloxacin and cephalosporins that it had already dealt with above.

The Panel noted that the claim appeared on a page headed 'Tazocin may decrease the incidence of MRSA' and above 'Substituting Tazocin for cephalosporins decreased the incidence of MRSA in one hospital', referenced to Smith. A bar chart illustrated the percentage reduction in MRSA isolates from 1994 (34%) to 1998 (23%) obtained in Smith. The Panel noted its comments and rulings above. Within the context of the page the claim 'Limiting the use of cephalosporins and ciprofloxacin is one means of minimizing the selection and dissemination of MRSA' implied that cephalosporins and ciprofloxacin were known to be significantly more likely to cause MRSA than Tazocin; that was not necessarily so and overstated the data. Breaches of the Code were ruled.

Upon appeal by Wyeth, the Appeal Board considered that the claim 'Limiting the use of cephalosporins and ciprofloxacins *is one* means of minimizing the selection and dissemination of MRSA' [emphasis added] was a true statement. It was sufficiently clear that the emergence of MRSA was a multifactorial process. The Appeal Board considered that together with the page heading 'Tazocin may decrease the incidence of MRSA' the statement at issue was not unreasonable. The Appeal Board ruled no breach of the Code.

Bayer plc, Pharmaceutical Division, complained about a 34 page booklet (ref ZTAZ680/0902) for Tazocin (piperacillin/tazobactam) issued by Wyeth Pharmaceuticals. Bayer supplied Ciproxin (ciprofloxacin).

Wyeth stated that the booklet was aimed at hospital doctors, including microbiologists, intensivists, oncologists, immunologists and those particularly familiar with antibiotic use. The intention was to help doctors treat a number of conditions where the causative organism was not immediately identified. In addition it addressed some of the problems associated with antibiotic resistance.

1 Page 5 – headed 'A confident choice in nosocomial pneumonia'

A sub-heading 'Tazocin monotherapy compares favourably with ciprofloxacin combination therapy in chest infections**' referenced to Wade *et al* (2000) appeared above a bar chart which depicted the percentage of patients with a complete / partial response to ciprofloxacin combination therapy (n=25) or Tazocin (n=35) at 72 hours (64% and 82.6% respectively, p=0.133) and those with a complete response at the end of the study (62.8% and 58% respectively, p=0.606).

The first bar chart was followed by a second sub-heading 'Tazocin combination therapy compares favourably with ceftazidime combination therapy in ventilator-associated pneumonia', referenced Brun-Buisson *et al* (1998) beneath which another bar chart compared, i*nter alia*, the clinical and bacteriological success rates of the two products; the p value for the statistical difference between the two was stated as p=ns. Beneath the key to this second bar chart was '** following liver transplantation' which referred to the results depicted in the first bar chart.

COMPLAINT

Bayer stated that the impression given by the heading on page 5 was that Tazocin had been used in all patients with chest infections, whereas the reference cited was in a select group of subjects following liver transplantation. It was possible to deduce this fact only by carefully searching the page for the ** legend which was placed at the bottom of the page, beneath a separate bar chart relating to a different study.

The presentation of the data was such as to exaggerate the role of Tazocin and to disparage ciprofloxacin contrary to Clauses 7.2, 7.3 and 7.10 of the Code. The differences between the outcomes of the regimens compared were not statistically significant, but unlike the subsequent bar chart on the same page neither bar chart was labelled as non-significant. This was misleading and thus in breach of Clause 7.2 of the Code.

The reference cited, Wade *et al* like many within the booklet was a poster submitted to a medical meeting and undue emphasis had been placed on preliminary data that had not been corroborated elsewhere in the medical literature. Bayer contended that this was contrary to the spirit of Clause 7.2.

RESPONSE

Wyeth stated that the allegation was firstly that the page heading 'A confident choice in nosocomial pneumonia' implied that the company had compared Tazocin with ciprofloxacin in <u>all</u> chest infections. There was no implication that Wyeth was claiming the use of Tazocin in all patients, rather for those with hospital-acquired lower respiratory tract infections (LRTIs). Similarly, Brun-Buisson *et al* referred to a 'population most probably having definite pulmonary infection acquired during mechanical ventilation'.

With reference to the double-starred footnote, there was no stipulation in the Code that such a footnote must appear immediately under the material to which it referred. Bayer commented that this reference could only be found by 'carefully searching' the page. Not only did the asterisks lead the physician to look to the place on the page where the clarification of use in liver transplants was given but also the reference was given for the relevant source document. Wyeth was aware that the revised Code due to appear later in 2003 would have new directions regarding footnotes.

Although the reference given here referred to patients with LRTIs following liver transplantation, there were other references which supported the claim that Tazocin was comparable to ciprofloxacin in the treatment of organisms responsible for LRTIs. For example, Sanguinetti *et al* (2000) demonstrated comparable susceptibility of organisms typically associated with LRTIs.

Furthermore, postmarketing surveillance of 7470 patients with moderate or severe infections treated with Tazocin had shown high response rates (Bodmann and Leitner, 2003). Over 90% of the patients had moderate or severe respiratory tract infections, intra-abdominal infections, skin / soft tissue infections and other infections. Eighty-five percent of the patients had concomitant diseases. Thirty-one percent had received previous antibiotic therapy, mostly cephalosporins and quinolones.

The heading 'Tazocin monotherapy compares favourably with ciprofloxacin combination therapy in chest infections' did not exaggerate the role of Tazocin. Wade *et al* concluded that 'empirical monotherapy with piperacillin / tazobactam was clinically highly efficacious, and just as effective as ciprofloxacin plus amoxicillin'. The aim of this heading was to show that the two treatments were comparable, and certainly not to disparage ciprofloxacin. Although patients involved in the study were post-transplant patients, the types of infections that were experienced were comparable to serious respiratory infections encountered by many patients in the general intensive care setting.

The p values 0.133 (at 72 hours) and 0.606 (at end of study) meant that there was no statistically significant difference between Tazocin monotherapy and ciprofloxacin in treating this type of chest infection, and there was no claim that one or the other was superior. A conclusion could therefore be drawn that there was no statistically significant difference between Tazocin and ciprofloxacin combination therapy. There was no claim made in the heading that there was any difference (statistically significant or otherwise) between the two products. The p values given were more meaningful than a statement regarding non-significant differences or an abbreviation such as 'ns'.

There was no requirement in the Code for references to be fully published papers. Posters could be cited, as could unpublished data ('data on file') as long as clear references were given. Statements made in promotional materials must be capable of substantiation as was this statement. Further to this, Wyeth was aware from discussion with Wade, the author, that the final results of this study had been submitted for publication to the Journal of

Antimicrobial Chemotherapy. The final results had come to the same conclusion as the initial data presented in the poster and there had been no new analysis. The paper had been resubmitted, following some amendments, and was awaiting acceptance by the journal. The conclusions drawn by Wade had not been disputed elsewhere in the medical literature.

PANEL RULING

The Panel noted that the data was referenced to Wade *et al* which compared Tazocin with ciprofloxacin plus amoxycillin for infective episodes in patients after orthotopic liver transplantation. The study concluded that empirical monotherapy with Tazocin was clinically highly efficacious and just as effective as ciprofloxacin plus amoxycillin. The abstract section stated that there were few studies available to guide rational selection of antibacterials for infection following liver transplantation.

The Panel noted that the heading referred to nosocomial pneumonia and the first sub-heading referred to chest infections. It was thus sufficiently clear that the data related to hospital-acquired LRTI. The Panel noted that the data was obtained in patients following orthotopic liver transplantation.

The patient population was described in a footnote at the bottom of the page in a very small typeface and immediately beneath the second, unrelated bar chart which depicted data from Brun-Buisson *et al*. The Panel noted that it was an established principle under the Code that otherwise misleading claims should not be qualified by footnotes.

The Panel considered that the bar chart at issue gave the impression that the data depicted applied to all patients with hospital-acquired lower respiratory tract infection which was not so. The data depicted was in patients following liver transplantation. The Panel noted the data submitted by Wyeth regarding the efficiency of Tazocin in the empiric treatment of LRTI in a wide range of patients including the data relating to those with ventilator-associated pneumonia shown on the same page of the detail aid. Nonetheless, the Panel considered that by not clearly stating that the specific results shown in the bar chart at issue related to liver transplant patients, the bar chart was misleading; readers were unable to judge the clinical significance of the data shown. Breaches of Clauses 7.2 and 7.3 were ruled. These rulings were appealed. The Panel did not consider the page exaggerated on this narrow point; no breach of Clause 7.10 was ruled.

The Panel noted that Wade *et al* concluded that Tazocin was just as effective as ciprofloxacin and amoxycillin. The Panel noted that the p values were stated in small print above each bar chart at 72 hours and end of the study. The Panel considered that the longer length bars depicted for Tazocin in the bar chart and the prominent greater percentage clinical response stated on each Tazocin bar than each ciprofloxacin bar gave the immediate visual impression that the difference between the products was statistically significant in favour of Tazocin and that was not so. This impression was compounded by the heading 'A confident choice in nosocomial pneumonia' and the sub-heading 'Tazocin monotherapy compares favourably with ciprofloxacin combination therapy in chest infections' (emphasis added). The Panel did not consider that the sub-heading showed that the two treatments were comparable as submitted by Wyeth. The presence of the non-significant p values was insufficient to negate the overall visual impression. The Panel considered that the presentation of the data was misleading and exaggerated the differences between the products; breaches of Clauses 7.2, 7.3 and 7.10 were ruled. These rulings were appealed.

The Panel noted that in the first bar chart on page 5 non-significant p values were stated with their numerical value; the second bar chart used the term p=ns to indicate non-significance. The Panel considered that although the abbreviations used were inconsistent they were not misleading in that regard. No breach of Clause 7.2 was ruled.

The Panel noted Bayer's comments about Wade *et al* in relation to the spirit of Clause 7.2 but did not consider that it had a complaint on this discrete issue and thus made no ruling upon it.

During its consideration of this case the Panel noted that this complaint was considered in relation to the requirements of the 2001 edition of the Code. The Panel noted Wyeth's submission that the 2003 edition of the Code would have new directions about footnotes. The Panel noted that whilst the supplementary information to Clause 7 of the 2003 edition of the Code stated that in general, claims should not be qualified by the use of footnotes and the like, this was not a newly introduced requirement, it merely reflected established interpretation of the Code.

APPEAL BY WYETH

Wyeth stated that the results obtained by Wade *et al* had been accepted for publication in the Journal of Antimicrobial Chemotherapy.

Wyeth maintained that the headline was not an 'otherwise misleading claim'. If it was not otherwise misleading, then it could not be 'corrected' or 'qualified' by a footnote. The bar charts, the statement and the claim could be substantiated.

Wyeth stated that Fowler *et al* (2003) had compared antipseudomonal penicillins plus ß-lactamase inhibitors (predominantly Tazocin although ampicillin-sulbactam was used 'sparingly') with fluoroquinolones (predominantly ciprofloxacin) in ventilator-associated pneumonia (VAP) of diverse aetiologies. VAP was synonymous with nosocomial pneumonia. Antipseudomonal penicillins plus ß-lactamase inhibitors were the only antimicrobial agent to emerge as a significant independent predictor of survival. Patients with clinically suspected VAP had lower in-hospital mortality if their initial regimen included antipseudomonal penicillins plus ß-lactamase inhibitors as compared to those patients who had not (hazard ratio of death 0.41; 95% CI 0.21 to 0.80; $p = 0.009$). Patients initially treated with fluoroquinolones had not had a statistically significant reduction in the relative hazard of death (hazard ratio of death 0.72; 95% CI 0.34 to 1.54; $p > 0.2$).

Wyeth submitted that the supplementary information for the 2003 Code stated: 'In general claims should not be qualified by the use of footnotes and the like'. However, the promotional piece was designed according to the 2001 Code which made no mention of footnotes in this regard.

Wyeth submitted that the ratio of the length of the 'at 72 hours' Tazocin bar (4.1cm) to that of the ciprofloxacin bar (3.1cm) was 1.3; the 'at 72 hours' Tazocin percentage 82.6% was 1.3 times larger than the ciprofloxacin percentage 64%. The ratio of the length of the 'end of study' Tazocin bar (3.2cm) to that of the ciprofloxacin bar (2.8cm) was 1.1; the 'end of study' Tazocin percentage 62.8% was 1.1 times larger than the ciprofloxacin percentage 56%. The bar charts were precisely proportional to the data represented. The artwork did not suggest that Tazocin was more effective than the evidence supported and did not imply a dramatic response to treatment. The (imaginary) axis was expressed in full, the scale was not unusual and there were no suppressed zeros. The presentation of the data was neither misleading nor exaggerated.

COMMENTS FROM BAYER

Bayer submitted that Wyeth's response had failed to address the issue raised in its original complaint, ie that the impression given in the piece was that Tazocin was as effective as ciprofloxacin in all patients with LRTI and on which point the Panel had already agreed.

Bayer also noted that in a previous Tazocin detail aid (ref ZTAZ 596/0900) this same data was presented in a manner which made it clear in the title that this data related only to patient infections following liver transplantation.

APPEAL BOARD RULING

The Appeal Board noted that the data was referenced to Wade *et al.* The patient population was described in a footnote beneath the second bar chart in a very small typeface. The Appeal Board noted that it was an established principle under the Code that otherwise misleading claims should not be qualified by footnotes.

The Appeal Board considered that the bar chart at issue gave the impression that the data depicted applied to all patients with hospital-acquired LRTI which was not so. The data depicted was in patients following liver transplantation. The Appeal Board noted that only one ciprofloxacin combination had been compared with Tazocin (ie ciprofloxacin + amoxicillin ± metronidazole) whereas in the clinical setting other ciprofloxacin combinations might be used depending on the patient and the antibiotic policy of the particular hospital. The Appeal Board considered that by not clearly stating that the data shown in the bar chart related to liver transplant patients, the bar chart was misleading; readers were unable to judge the clinical significance of the data shown. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.3. The appeal on this point was unsuccessful.

The Appeal Board noted that the bar chart showed a numerical advantage in favour of Tazocin vs ciprofloxacin for percentage clinical response. The Appeal Board considered that despite the p values showing that there was no statistically significant difference between Tazocin and ciprofloxacin the overall impression was one of superiority for Tazocin. This impression was compounded by the heading 'A confident choice in nosocomial pneumonia' and the sub-heading 'Tazocin monotherapy compares favourably with ciprofloxacin combination therapy in chest infections' (emphasis added). The Appeal Board did not consider that the sub-heading showed that the treatments were comparable as submitted by Wyeth. The Appeal Board considered that favourably might be interpreted as better than which was not a fair reflection of the data. The presence of the non-significant p values was insufficient to negate the overall visual impression. The Appeal Board considered that the presentation of the data was misleading and exaggerated the differences between the products. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2, 7.3 and 7.10. The appeal on this point was unsuccessful.

2 Page 20 headed 'Tazocin is well tolerated in clinical practice ...'

The claims 'Unlike ciprofloxacin, Tazocin can be administered by bolus injection as well as infusion' and 'Tazocin has a low propensity to cause superinfection:' appeared in emboldened print. The latter claim was followed by 3 bullet points, the third of which read '-Less likely to lead to MRSA than ciprofloxacin or cephalosporins'.

COMPLAINT

Bayer stated the claims were made regarding tolerability of Tazocin in clinical practice. The claim 'Unlike ciprofloxacin, Tazocin can be administered by bolus injection as well as infusion' had nothing to do with tolerability and was intended to cause doubt in the mind of clinicians regarding ciprofloxacin. The claim was exaggerated and intended to discredit ciprofloxacin contrary to Clauses 7.2 and 7.3 of the Code.

On the same page there was a bold heading that 'Tazocin has a low propensity to cause superinfection:' which appeared above the statement that Tazocin was 'Less likely to lead to MRSA than ciprofloxacin or cephalosporins' citing Smith (1999).

Smith referred to changes in antibiotic use in community medical centers in the USA and indicated that a decrease in resistance between 1994 and 1998 was 'attributable to a cohesive working relationship between pharmacists, microbiologists and infectious diseases physicians and personnel and a decision to decrease administration of cephalosporins in favour of piperacillin-tazobactam'. The paper indicated that the purpose of the programme was 'to determine if reductions in administration of cephalosporin, imipenem and vancomycin could favorably affect gram-negative resistance'. In the results section the author indicated that 'ciprofloxacin and ampicillin-

sulbactam use remained relatively constant'. The only mention of ciprofloxacin and MRSA was in the discussion, where Hill *et al* (1998) was quoted as stating 'One report stated that either ciprofloxacin or a cephalosporin was significantly associated with acquisition of MRSA'.

Hill *et al* was a letter to a journal and indicated the uncorroborated results of a 'small pilot study' which suggested that limiting the use of cephalosporins and ciprofloxacin was one means of minimising selection and dissemination of MRSA. Whilst indicating that administration of ciprofloxacin or a cephalosporin was significantly associated with acquisition of MRSA, the authors also stated 'It is not clear why some antibiotics to which MRSA strains are resistant influence colonization more than others'. Neither this reference, nor the one cited within the text of the page supported the contention that Tazocin was less likely to lead to MRSA than the two antibiotics mentioned. Breaches of Clauses 7.2 and 7.3 of the Code were alleged.

Bayer alleged that by oversimplification of a very complex topic of antibiotic resistance in an attempt to denigrate ciprofloxacin, Wyeth was in breach of Clause 7.10. Livermore (2000) discussed the epidemiology of antibiotic resistance and acknowledged that EMRSA strains 15 and 16 were epidemic in the UK. Bayer accepted that resistance to ciprofloxacin was mediated via these strains, but pointed out that Livermore indicated these two strains might be different and might have a greater ability to colonise and thus spread infection. Livermore stated though both strains were quinolone resistant and might have been advantaged by use of quinolones that it was a tenuous argument given the propensity of mutational resistance in any *Staphylococcus aureus* strains. Wyeth had therefore failed to present a full and balanced account of the resistance issue and was in breach of Clause 7.10 with this exaggerated and all embracing statement.

RESPONSE

Wyeth stated that the claim 'Unlike ciprofloxacin, Tazocin can be administered by bolus injection as well as infusion' was a factual statement based on the methods of administration cited in both the Ciproxin and Tazocin summaries of product characteristics (SPCs).

The method of administration related to tolerability in that patients subject to fluid restriction would be likely to have fewer side effects when given a bolus injection as opposed to being given a larger amount of fluid by infusion. Tazocin could be given either as a bolus injection or as an infusion, whereas ciprofloxacin could only be given as an infusion. The dosage range of ciprofloxacin for adults was 100-400mg twice daily, but the recommended dosage for severe infections (as referenced in the current Ciproxin detail aid) was 200-400mg twice daily. This amounted to a volume of 200-400ml of fluid daily. The recommended dosage of Tazocin was 4.5g three times daily for the majority of infections, or 4.5g four times daily for febrile neutropenia. If given by bolus injections, this amounted to a volume of 60-80ml daily. This fact was of particular relevance in the treatment of many critically ill, intensive care or renal patients, who were frequently restricted as to the volume of fluids they could receive. As a result, the administration of Tazocin as an intravenous bolus was seen as more tolerable. As this was a factual statement of comparison, there was no exaggerated claim, or any way that this could be seen to discredit ciprofloxacin.

In relation to the statements 'Tazocin has a low propensity to cause superinfection' and 'Less likely to lead to MRSA than ciprofloxacin', Wyeth stated that in 1997 at the Methodist Hospital in Indianapolis the prevalence of MRSA was 23% of all *Staphylococcus aureus* isolates at the time when Tazocin was by far and away the predominant antibiotic in use. Smith *et al* was cited to establish this fact. There were a number of studies indicating that ciprofloxacin was associated with MRSA: Daum *et al* (1990), Graffunder and Venezia (2002).

Crowcroft *et al* (1999) was closely tied in with Smith *et al* and was conducted in 50 Belgian hospitals between 1994 and 1995 and showed that the incidence of nosocomial MRSA increased with increasing use of quinolones ($p=0.05$). This phenomenon had also been reported in Germany; Manhold *et al* (1998) and Dziekan *et al* (2000).

The booklet at issue could legitimately have stated 'Tazocin less likely to lead to MRSA than ciprofloxacin' or 'Ciprofloxacin has a high propensity to cause superinfection' – neither of which it did. There was a wealth of evidence to support the claim that increased use of ciprofloxacin led to the increased rate of MRSA. In the light of the above, Wyeth believed that the claims in the Tazocin booklet were not unbalanced, unfair, misleading or exaggerated.

The issue that Wyeth addressed in its comments about the oversimplification of antibiotic resistance in an attempt to denigrate ciprofloxacin was that changing antibiotic use could change antimicrobial resistance patterns. Any suggestion that this was oversimplifying the issue was addressed by Smith *et al* which gave a more global overview of the subject of antimicrobial resistance, as did Livermore. Once again, there was no attempt to denigrate ciprofloxacin in this or any other section of the booklet, and further references were available to support Wyeth's claims regarding antimicrobial resistance. Wyeth had referenced supporting literature that gave a more detailed discussion of this subject area. There were several other references available in the medical literature.

Although Livermore indicated that the resistance issue was multifactorial, it nevertheless, focused on genetic and mutational factors related to fluoroquinolones. Furthermore, Livermore stated 'Fluoroquinolones initially were perceived as active against methicillin-resistant staphylococcal infections, with most MRSA not resistant'. A promotional piece such as the booklet in question was not the appropriate arena to discuss fully the subject of antibiotic resistance and the issues associated with this. The statements made were not considered exaggerated or all embracing, as they included issues

associated with antibiotic resistance widely discussed throughout the current literature, and capable of substantiation by the reference used.

PANEL RULING

The Panel noted that the claim 'Unlike ciprofloxacin, Tazocin can be administered by bolus injection as well as infusion' appeared on a page headed 'Tazocin is well tolerated in clinical practice …'. The Panel noted Wyeth's submission that the method of administration related to tolerability as patients subject to fluid restriction would be less likely to have side effects if administered a bolus injection than an infusion. The Panel considered that the claim at issue, which appeared in an emboldened typeface on a page which discussed tolerability, gave the impression that ciprofloxacin was generally less well tolerated than Tazocin due to its mode of administration. The claims were referenced to the respective products' SPCs neither of which discussed mode of administration in relation to tolerability. The Panel considered that in the context in which it was used the claim was misleading. Breaches of Clauses 7.2 and 7.3 were ruled. These rulings were appealed.

The Panel noted that the claim 'Less likely to lead to MRSA than ciprofloxacin or cephalosporins' referenced to Smith appeared beneath an emboldened subheading 'Tazocin has a low propensity to cause superinfection'. Smith reported on a four year hospital programme designed to determine if reductions in administration of cephalosporin, imipenem and vancomycin could favourably affect, *inter alia*, MRSA. The overall resistance of MRSA reduced from 34% to 23%. Smith stated that the reduction in MRSA was difficult to explain but noted that Hill *et al* (1998) had stated that either ciprofloxacin or a cephalosporin was significantly associated with acquisition of MRSA. Hill *et al*, a letter, reported a small pilot study in 17 patients colonized and/or infected with MRSA which concluded that the results suggested that 'limiting the use of cephasporins and ciprofloxacin is one means of minimizing the selection or dissemination of [MRSA]'. A larger study to confirm these findings was being undertaken.

Other studies had also suggested a link between ciprofloxacin and the emergence of MRSA. Crowcroft *et al* showed a positive and independent association between the incidence of MRSA in hospitals and use of, *inter alia*, quinolones. Ciprofloxacin was one of nine quinolones used in the study. The study authors stated that their findings should be interpreted with caution; they had shown association not cause. The authors suggested ways in which future studies could produce more robust results.

Manhold *et al* stated that ciprofloxacin could have played a role in the outbreaks of MRSA seen in some cardiac surgery patients and Dziekan *et al* suggested that fluoroquinolone use might be a factor in the transmission of MRSA and should be prescribed with prudence in hospitals where MRSA was endemic.

The Panel noted that the booklet was aimed at hospital doctors who would be very familiar with the issues of antibiotic use and resistance, particularly MRSA. The Panel noted that there was data suggesting a link between ciprofloxacin and MRSA. The claim at issue, however, suggested that the risks of MRSA emerging with Tazocin therapy and those associated with ciprofloxacin therapy were known and that there was a significant difference, in favour of Tazocin, between the two. This was not so. The Panel considered that the claim 'Less likely to lead to MRSA than ciprofloxacin and cephalosporins' overstated that data and was misleading in that regard. Breaches of Clauses 7.2 and 7.3 were ruled. These rulings were appealed.

Livermore examined the epidemiology of antibiotic resistance and stated that the reasons for the epidemic success of some resistant strains remained obscure. Many factors potentially contributed to the spread and persistence of individual clones. The Panel noted its comments on Smith above and its ruling on the claim 'Less likely to lead to MRSA than ciprofloxacin or cephalosporin'. The Panel considered that the section headed 'Tazocin has a low propensity to cause superinfection' oversimplified the issue of superinfection. It was not a fair reflection of the data and was exaggerated in this regard; a breach of Clause 7.10 was ruled. This ruling was appealed.

APPEAL BY WYETH

Wyeth noted that the Pharmaceutical and Medical Abbreviations Dictionary defined 'tolerance' as 'the ability to endure unusually large doses of a drug or toxin' derived from the Latin 'tolerantia'. An article from the Bayer Corporation relating to the administration of intravenous immunoglobulin G (IVIg) provided a helpful example of the phenomenon of tolerability (Lemm, 2002): 'Tolerability is a measure of the ability of a patient to receive a formulation of IVIg without infusion-related adverse events. Tolerability varies markedly among IVIg preparations and patient populations. Older patients, for example, or those with cardiovascular disease, may be less tolerant of preparations that have high osmolality or require larger volumes'.

Wyeth submitted that the reference to the two SPCs was provided to establish the modes of administration of the two antibiotics in question, Tazocin (by bolus and infusion) and ciprofloxacin (by infusion only). The maximal recommended dose of ciprofloxacin, 400mg twice daily, involved the administration of two infusions of 200ml of fluid each over 1 hour; a total of 2 hours per day. The maximal recommended dose of Tazocin, 4.5g four times daily, involved the administration of four 5 minute boluses; a total of 20 minutes per day.

Both SPCs had discussed the mode of administration in relation to tolerability. That for ciprofloxacin stated: 'Dosage adjustments are not usually required, except in patients with severe renal impairment (serum creatinine >265 micromole/l or creatinine clearance <20ml/minute). If adjustment is necessary, this may be achieved by reducing the total daily dose by half, although monitoring of drug serum levels provides the most reliable basis for dose adjustment'.

The Tazocin SPC stated: 'In patients with renal insufficiency, the intravenous dose should be adjusted

to the degree of actual renal impairment. The suggested daily doses are as follows:

Creatinine Clearance (ml/min)	Recommended Piperacillin/ Tazobactam Dosage
20-80	12g / 1.5g / day Divided Doses 4g / 500mg q 8H
<20	8g / 1g / day Divided Doses 4g / 500mg q 12H

For patients on haemodialysis, the maximum daily dose is 8g / 1g piperacillin / tazobactam. In addition, because haemodialysis removes 30%-50% of piperacillin in 4 hours, one additional dose of 2g / 250mg piperacillin / tazobactam should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of Tazocin will provide additional guidance for adjusting dosage.'

Wyeth submitted that when the types of patients receiving either antibiotic intravenously were considered (eg severely ill, intensive care, fluid restricted, renal failure, etc) it was more 'tolerable' to have the option of bolus and infusion rather than solely infusion. Therefore, the claim was not misleading.

Wyeth submitted that a great deal was known about the mechanisms, the risks and the differences (Lowy, 2003), with mechanisms acting across the antibiotic classes. Graffunder and Venezia stated: 'Multiple logistic regression analysis identified six risk factors that were associated independently with MRSA infection. These risk factors were previous hospitalisation, longer length of stay before infection, surgery, enteral feedings, levofloxacin use and macrolide use'. The odds ratio by multiple logistic regression analysis for the association between MRSA and the fluoroquinolone levofloxacin was 8.01 (95% CI 3.15 to 20.3, $p<0.001$). The OR for ß-lactam / ß-lactamase inhibitor combinations by univariate analysis was 2.3 (95% CI 1.4 to 3.6, $p<0.001$). ß-lactam antibiotics were combined as a class to ensure that any effect was not diluted. In Dziekan *et al* there was a univariate analysis of the association of potential risk factors for MRSA acquisition in hospital. The crude OR for ß-lactams was 3.4 (95% CI 1.53 to 7.43, $p=0.001$) whilst that for fluoroquinolones was 7.3 (95% CI 2.19 to 24.5, $p<0.001$). Stratifying by antibiotic group improved the analysis and fluoroquinolone usage emerged as an independent risk factor ($p=0.025$).

Wyeth submitted that the claim that Tazocin was 'Less likely to lead to MRSA than ciprofloxacin or cephalosporins' did not overstate the data and was not misleading. Furthermore, the claim was not an oversimplification if one took into consideration the many antibiotics that could potentially be responsible for the emergence of MRSA. Of those many antibiotics, Livermore only mentioned two – fluoroquinolones and third-generation cephalosporins. Livermore stated: 'Fluoroquinolones initially were perceived as active against methicillin-resistant *Staphylococcus aureus* (MRSA) but staphylococci have an endogenous efflux pump and resistance arises if this is up-regulated by mutation at *norA*. The result is that ciprofloxacin has had disappointing efficacy against staphylococcal infections, with most MRSA now resistant'.

COMMENTS FROM BAYER

Bayer stated that it understood the point Wyeth had made in its appeal about fluid balance and the clinical decisions that needed to be taken when prescribing IV antibiotics in certain patient groups. The fact that Tazocin could be administered as a bolus was clear but stating this attribute in bold, under a section about tolerability gave prescribers the impression that Ciproxin was generally less well tolerated than Tazocin which was an unbalanced and misleading claim intended to discredit Ciproxin. Unlike Tazocin, Ciproxin was available in tablets but Bayer could not claim that Ciproxin was better 'tolerated' than Tazocin because of that.

Bayer alleged that as in point 1 above, it had also noted that the tolerability claim at issue was not made on the comparable page in the previous Tazocin detail aid (ref ZTAZ 596 / 0900).

Bayer stated that a comparison of the previous and current Tazocin detail aids led it to consider that the previous version had been modified to specifically target Ciproxin. Bayer alleged that these modifications had been carried out to promote Tazocin in a way which was not balanced, fair and objective and which misled and created doubt about Ciproxin in the minds of prescribers.

Bayer noted that two of the three papers quoted in Wyeth's appeal (Graffunder and Venezia and Dziekan *et al*) were the same papers quoted in its first response. The Panel would already have assessed this information before reaching its conclusion that Wyeth's claim overstated the data, was misleading and oversimplified the issue of superinfection in relation to Ciproxin.

Bayer noted that the third paper (Lowy) discussed antibiotic resistance mechanisms in general but did not compare the risks and differences of using Tazocin or Ciproxin with regard to the emergence of MRSA.

Bayer alleged that no new data had been put forward to substantiate Wyeth's claim.

APPEAL BOARD RULING

The Appeal Board considered that the claim 'Unlike ciprofloxacin, Tazocin can be administered by bolus injection as well as infusion' which appeared on a page headed 'Tazocin is well tolerated in clinical practice …', gave the impression that ciprofloxacin was generally less well tolerated than Tazocin due to its method of administration. The claim was referenced to the respective products' SPCs neither of which discussed method of administration in relation to tolerability. The Appeal Board considered that in the context in which it was used the claim was misleading. The Appeal Board upheld the Panel's

ruling of breaches of Clauses 7.2 and 7.3. The appeal on this point was unsuccessful.

The Appeal Board noted that the claim 'Less likely to lead to MRSA than ciprofloxacin or cephalosporins' referenced to Smith appeared beneath an emboldened subheading 'Tazocin has a low propensity to cause superinfection'. Smith had reported that as a result of reductions in administration of cephalosporin, imipenem and vancomycin the overall resistance of MRSA reduced from 34% to 23%. However, the Appeal Board noted that Smith had stated that the reduction in MRSA was difficult to explain but cited Hill *et al* in support of his findings. The Appeal Board noted Hill *et al* had stated that of the patients who had received only ciprofloxacin the incidence of MRSA was not significantly different from that of the control.

The Appeal Board noted other studies, Crowcroft *et al*, Manhold *et al* and Dzeikan *et al* had indicated that there might be an association between quinolone administration and emergence of MRSA, but had exercised caution in their conclusions.

The Appeal Board noted that there was data suggesting a link between ciprofloxacin therapy and MRSA. The claim at issue, however, suggested that the risks of MRSA emerging with Tazocin therapy and those associated with ciprofloxacin therapy were known and that there was a significant difference, in favour of Tazocin, between the two. This was not so. The Appeal Board considered that the claim 'Less likely to lead to MRSA than ciprofloxacin and cephalosporins' overstated that data and was misleading in that regard. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.3. The appeal on this point was unsuccessful.

The Appeal Board noted that Livermore had examined the epidemiology of antibiotic resistance and stated that the reasons for the epidemic success of some resistant strains remained obscure. Many factors potentially contributed to the spread and persistence of individual clones. The Appeal Board noted its comments on Smith above and its ruling on the claim 'Less likely to lead to MRSA than ciprofloxacin or cephalosporin'. The Appeal Board considered the heading 'Tazocin has a low propensity to cause superinfection' implied an absolute, rather than a relatively low likelihood to lead to MRSA and yet there was no data to support such an implication.

In addition the Appeal Board noted that ciprofloxacin was widely used in the community whereas Tazocin was not. Pre-exposure to ciprofloxacin in the community might be a factor in the potential for a patient to develop MRSA in hospital.

The Appeal Board considered that the section headed 'Tazocin has a low propensity to cause superinfection' oversimplified the issue of superinfection. It was not a fair reflection of the data and was exaggerated in this regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.10. The appeal on this point was unsuccessful.

3 Claim 'The incidence of MRSA is growing, with the usage of fluoroquinolones in human and animals fuelling the problem of resistance'

This claim appeared on page 22 and was referenced to Hooper (2001) and McKellar (2001). Page 22 was headed 'MRSA is a growing problem'.

COMPLAINT

Bayer alleged that the claim at issue was exaggerated and all-embracing, in breach of Clause 7.10 of the Code. Livermore indicated that the resistance issue was multifactorial and could not be simplified to a single headline. Bayer further alleged that Wyeth had thus indirectly disparaged ciprofloxacin contrary to Clause 7.2.

RESPONSE

Wyeth stated that the claim that the incidence of MRSA was growing was clearly documented. Recent figures indicated that the UK had one of the highest rates of MRSA within Europe, with rates increasing steadily over recent years. A 2002 report from the European Antimicrobial Resistance Surveillance Survey (EARSS) had shown an increase in the prevalence of methicillin / oxacillin resistance in the UK, increasing at a rate of approximately 6% per year. The reports for 2001 showed prevalence rates of 45% in blood isolates from the UK.

Hooper and McKellar substantiated the argument that the use of fluoroquinolones in humans and animals was fuelling the problem of resistance. Indeed, in another publication, produced by Bayer entitled 'Guidelines for the use of quinolones in veterinary medicine' (Jong and Mörner, 2002), Bayer itself discussed the issues regarding over use of quinolones potentially leading to increased resistance.

'The use of antimicrobial agents such as quinolones can lead to the selection of resistant forms of bacteria'…'It is sometimes postulated that the use of antibiotics in veterinary medicine may compromise human health if resistant bacteria develop in animals and are transferred to people via the food chain or the environment. This is of particular concern for highly valuable classes of antibiotics such as the quinolones. The possible development of resistance to quinolones is constantly followed by the media with more than usual interest'… 'As the issue of resistance in people is of utmost importance and potential risks have not yet been fully quantified, Bayer has established a clear framework of precautions, extending the earlier 'Bayer's guidelines' for responsible use of quinolones'… 'Prudent use of quinolones is important to reduce selection and dissemination of resistance'.

These references and others reflected the overall conclusions of the claim at issue which was not exaggerated or all-embracing. In addition, there were other references that could be used to support the claims regarding ciprofloxacin and resistance patterns: for example Webber and Piddock (2001), from the Division of Immunity and Infection, University of Birmingham, which stated, 'Quinolone resistant *Escherichia coli* in animals have increased in numbers after quinolone introduction in a number of different case studies. The resistance mechanisms in these isolates are the same as those in resistant strains found in humans. Care needs to be taken to ensure

that quinolones are used sparingly and appropriately as highly resistant strains of *Escherichia coli* can be selected and may pass into the food chain'.

PANEL RULING

The Panel noted that the claim at issue was referenced both to Hooper and to McKellar. Hooper stated that resistance in *Campylobacter jejuni* had been associated with both human quinolone use and the rising occurrence of resistant campylobacters in food animals, particularly poultry. McKellar considered the impact that fluoroquinolone use in veterinary medicine had had in global resistance emergence and concluded that such use had resulted in resistance in animal bacterial populations. Greatest concern was that resistant organisms were transmitted to man where they proved difficult to treat. Campylobacters selected for resistance in poultry posed a particular threat. The risk to man associated with this threat had not been quantified and there was likely to be ongoing debate regarding the acceptable risk.

The Panel noted its comments at point 2 in relation to the claim 'Less likely to lead to MRSA than ciprofloxacin or cephalosporins'. The Panel considered that the claim 'The incidence of MRSA is growing, with the use of fluoroquinolones in humans and animals fuelling the problem of resistance' gave the impression that use of fluoroquinolones in humans and animals was the main driver and that was not necessarily so. There was some evidence regarding the use of fluoroquinolones in animals and the possible transfer of resistant organisms to humans but not MRSA *per se*. The emergence of MRSA in humans was multifactorial. The claim overstated the data and was thus misleading and exaggerated the role of fluoroquinolones, including ciprofloxacin as alleged. Breaches of Clauses 7.2 and 7.10 were ruled. These rulings were appealed.

APPEAL BY WYETH

Wyeth submitted that the emergence of MRSA in humans was multifactorial (Haddadin *et al*, 2002). Intrinsic antibiotic resistance genes might be selected in the absence of antibiotic pressure (Alonso *et al*, 2001): 'Several antibiotic resistance determinants have a primary physiological role other than antibiotic resistance. In fact, they have been selected for metabolic, biosynthetic or signalling purposes. However, once antibiotic selective pressure is applied, mutants that overproduce these determinants can be selected in this way, reinforcing their adaptive role as antibiotic resistance determinants'. Selective *non-antibiotic* environmental pressure might also occur on *acquired* antibiotic resistance.

Wyeth submitted with reference to the second and third rulings in point 2 above describing the links between MRSA and fluoroquinolones in humans, that the scope of the claim was limited to the role of antibiotics in the development of MRSA rather than that of other factors such as age, hospitalisation, surgery or open skin lesions (Lucet *et al*, 2003).

Wyeth submitted that for humans, MRSA was primarily a problem in the hospital setting and this had been covered in the above point. Hooper, to which the claim was referenced, stated: 'Emergence of fluoroquinolone resistance in human bacterial pathogens has been associated with human use of quinolones. Variations in rates of emergence among different species have been affected by both mechanistic and epidemiologic factors. Rates of resistance rose earliest in Staphylococcus aureus, greatest in methicillin-resistant strains (MRSA) and Pseudomonas aeruginosa, both of which can become resistant after single mutations. In MRSA, co-selection and nosocomial spread further contributed to a particularly rapid rise'.

Wyeth submitted that non-antibiotic related environmental factors might be fuelling antibiotic resistance in animals. But it was the *antibiotic* related factors fuelling antibiotic resistance in animals that was the focus of the apparent breach. In particular, it was the impression that the role of fluoroquinolones had been overstated or exaggerated that constituted the apparent breach. The statement in question did not necessarily claim that the usage of fluoroquinolones in animals fuelled the emergence of MRSA resistance in humans.

Wyeth noted that Swartz (2002) had stated: 'Many lines of evidence link antimicrobial-resistant human infections to foodborne pathogens of animal origin. Types of evidence reviewed include: 1. direct epidemiologic studies; 2. temporal evidence; 3. additional circumstantial evidence; 4. trends in antimicrobial resistance among Salmonella isolates; and 5. trends in antimicrobial resistance among other pathogens, such as *Campylobacter jejuni*'.

O'Brien (2002) had stated: 'A bacterial isolate at any place may thus be resistant, not only because nearby use of antimicrobials had amplified such a genetic construct locally, but also because distant use had caused the construct or its components to evolve in the first place and spread there'.

Wyeth noted that according to Webber and Piddock quinolones were currently licensed for a wide range of species worldwide including cattle, swine, chickens, turkeys, fish, dogs and cats. Quinolones might be administered orally. Wyeth conceded that the main impact of veterinary quinolones on microbial resistance was on *Campylobacter* spp. and *Salmonella* spp. (Witte, 1998; Ferber, 2000). However, Wyeth maintained that *Staphylococcus aureus*, including MRSA, could and had infected livestock and other animals, including domestic pets, and details were provided.

Wyeth further noted that transmission of MRSA from humans to animals appeared to be a danger (Seguin *et al*, 1999). Here, on the basis of pulsed-field gel electrophoresis (PFGE) and other identity tests, the staff of a veterinary teaching hospital appeared to be the primary source of infection for 11 horses undergoing various diagnostic and surgical procedures, although the specific mode of transmission was unclear.

Wyeth submitted that neither piperacillin nor Tazocin were licensed for use in animals and there were no veterinary or oral preparations. Therefore Tazocin could not be fuelling antibiotic resistance problems in animals while fluoroquinolones could.

COMMENTS FROM BAYER

Bayer alleged that in Wyeth's appeal, references provided only a background to the issues surrounding the use of antibiotics in humans and animals, the development of resistant strains and the possibilities of some strains cross-infecting humans and animals. Wyeth's list of references did not present new data to support its claim that fluoroquinolone use fuelled the development of MRSA over and above other antibiotic classes. However, Bayer noted that Bojkova and Stevanov stated:

'Isolation of MRS from milk and meat products and the presented results about their resistance to Oxacillin and Teicoplanin lead to the conclusion that the use of ß-lactam antibiotics in veterinary practice have to be controlled because of the possibility for their transmission from animals to men by foodstuff.'

Bayer noted that piperacillin belonged to the ß-lactam class of antibiotics.

Like Tazocin, Ciproxin was also not licensed for use in animals anywhere in the world. Bayer accepted that in certain countries Ciproxin might be used in animals but so might piperacillin/Tazocin. In fact, guidelines for the use of piperacillin/Tazocin in animals were available in this country (Small Animal Formulary, 1999).

Bayer alleged that it was hard to reach any conclusion other than that Wyeth had oversimplified antibiotic resistance issues and had overstated the data to support the promotion of Tazocin. Wyeth's argument was misleading and exaggerated the role of fluoroquinolones as opposed to any other antibiotic class in this very complex area.

APPEAL BOARD RULING

The Appeal Board noted that the claim at issue was referenced to both Hooper and McKeller which had investigated resistance in *Campylobacter jejuni* after treatment with quinolones and fluroquinolones and not MRSA *per se*.

The Appeal Board noted its comments at point 2 in relation to the claim 'Less likely to lead to MRSA than ciprofloxacin or cephalosporins'. The Appeal Board considered that the claim 'The incidence of MRSA is growing, with the use of fluoroquinolones in humans and animals fuelling the problem of resistance' gave the impression that use of fluoroquinolones in humans and animals was the main driver and that was not necessarily so. The emergence of MRSA in humans was multifactorial. The claim overstated the data and was thus misleading and exaggerated the role of fluoroquinolones, including ciprofloxacin as alleged. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.10. The appeal on this point was unsuccessful.

4 Claim 'Limiting the use of cephalosporins and ciprofloxacin is one means of minimising the selection and dissemination of MRSA'

This claim appeared on page 23 beneath the heading 'Tazocin may decrease the incidence of MRSA' and was referenced to Hill *et al* (1998).

COMPLAINT

Bayer stated that this was a repetition of the all-embracing claim about limitation of use of ciprofloxacin and cephalosporins that it had already dealt with above at points 2 and 3. Bayer alleged breaches of Clauses 7.2, 7.3, and 7.10 of the Code.

RESPONSE

Wyeth referred to its comments above and also stated that despite the fact that this was a 'small pilot study' (Smith) it was nevertheless the case that all 17 (100%) of the MRSA isolates were resistant to ciprofloxacin. Furthermore the study also showed that 'either ciprofloxacin or a cephalosporin had been administered to 14 (82.3%) of the MRSA patients compared with only 4 (23.5%) of the patients in the control group; this difference is highly significant ($p=0.01$)'. The isolation of MRSA at that hospital would not lead a clinician to utilise ciprofloxacin as the antibiotic of first choice at present. It might, however, lead the clinician to believe that ciprofloxacin might regain usefulness if its use was limited.

PANEL RULING

The Panel noted that the claim appeared on a page headed 'Tazocin may decrease the incidence of MRSA' and above 'Substituting Tazocin for cephalosporins decreased the incidence of MRSA in one hospital', referenced to Smith. A bar chart illustrated the percentage reduction in MRSA isolates from 1994 (34%) to 1998 (23%) obtained in Smith. The Panel noted its comments and rulings at points 2 and 3 above. Within the context of the page the claim 'Limiting the use of cephalosporins and ciprofloxacin is one means of minimizing the selection and dissemination of MRSA' implied that cephalosporins and ciprofloxacin were known to be significantly more likely to cause MRSA than Tazocin; that was not necessarily so and overstated the data. Breaches of Clauses 7.2, 7.3 and 7.10 were ruled. These rulings were appealed.

APPEAL BY WYETH

Wyeth submitted that if points 2 (second and third rulings) and 3 (above) were accepted then the claim was valid and not an overstatement.

COMMENTS FROM BAYER

Bayer agreed with Wyeth that point 4 was covered by the arguments in points 2 (second and third rulings) and 3 (above).

Bayer, in summary, alleged that this piece fell well below the standards required by the Code and it was surprised that Wyeth had chosen to appeal against the Panel's decisions. In Bayer's opinion none of the new data submitted in Wyeth's response supported its original claims.

APPEAL BOARD RULING

The Appeal Board considered that the claim 'Limiting use of cephalosporins and ciprofloxacins **is one** means

of minimizing the selection and dissemination of MRSA' [emphasis added] was a true statement. It was sufficiently clear that the emergence of MRSA was a multifactorial process. The Appeal Board considered that together with the page heading 'Tazocin may decrease the incidence of MRSA' the statement at issue was not unreasonable. The Appeal Board ruled no breach of Clauses 7.2, 7.3 and 7.10. The appeal on this point was successful.

Complaint received **30 April 2003**

Case completed **30 September 2003**

CASE AUTH/1460/5/03

LUNDBECK v WYETH

Promotion of Efexor XL

Lundbeck complained about an Efexor XL (venlafaxine) detail aid and four leavepieces issued by Wyeth. Lundbeck supplied Cipramil (citalopram) and Cipralex (escitalopram).

Lundbeck noted that the claim in the detail aid 'Start with the best odds of reaching remission Superior efficacy versus SSRIs and antidepressants overall' was referenced to Smith *et al* (2002), and in the leavepieces the claim 'Efexor XL is superior to the SSRIs in helping patients reach remission' was additionally referenced to Thase *et al* (2001). Lundbeck alleged that the claims were all embracing and inaccurately supported by the references as the studies failed to include various licensed and widely available treatments for depression (such as citalopram, escitalopram, nefazodone and reboxetine). Lundbeck noted that Montgomery *et al* (2002) had compared escitalopram with venlafaxine in depression and demonstrated similar overall efficacy with benefits for escitalopram in terms of remission.

The Panel noted that Smith *et al* was a systematic review of 32 double-blind, randomized trials (n=5562) comparing venlafaxine with tricyclic antidepressants (TCAs) (clomipramine, imipramine, dothiepin and amitriptyline), SSRIs (fluoxetine, fluvoxamine, paroxetine and sertraline) and other antidepressants (trazodone and mirtazapine) in the treatment of depression. The Panel noted that venlafaxine had thus not been compared to every possible other antidepressant as suggested by the claim in question. For example, no trials of venlafaxine versus doxepin, a tricyclic antidepressant, or citalopram, an SSRI, or reboxetine had been included. No monoamine-oxidase inhibitors (MAOIs) had been included.

Smith *et al* showed an advantage for venlafaxine compared with fluoxetine, paroxetine, sertraline and the SSRIs overall but not compared with fluvoxamine. Compared with the other antidepressants (mirtazapine and trazodone) there was no advantage for venlafaxine and only a slight advantage when compared with the tricyclic antidepressants. When the results from all of the studies were pooled there was an advantage for venlafaxine.

The Panel noted that one of the limitations stated by Smith *et al* was that apart from the comparison with fluoxetine, there were insufficient comparisons between venlafaxine and individual SSRIs and other antidepressants to draw strong conclusions with regard to specific comparisons. The authors also considered that further studies were required to determine how generalisable their results were to different settings and whether venlafaxine had increased effectiveness in usual clinical practice.

The Panel considered that the claim 'Start with the best odds of reaching remission Superior efficacy versus SSRIs and antidepressants overall' was a broad, unequivocal claim that Efexor XL had greater antidepressant efficacy than every SSRI and all other antidepressants. The Panel considered that the claim was exaggerated and did not reflect the data accurately. Breaches of the Code were ruled. Upon appeal by Wyeth, the Appeal Board upheld the Panel's rulings.

The claim in the leavepieces, 'Efexor XL is superior to the SSRIs in helping patients reach remission' was referenced to Smith *et al* and Thase *et al*. Thase *et al* pooled data from 8 studies of major depressive disorder to compare remission rates during treatment with venlafaxine or SSRIs (fluoxetine; paroxetine; fluvoxamine). Thase *et al* stated that one of the limitations of the study was that there were not a sufficient number of studies to compare venlafaxine with specific SSRIs other than fluoxetine. The Panel noted that, as in Smith *et al*, no comparisons of venlafaxine with either citalopram or escitalopram had been included.

The Panel considered that the claim 'Efexor XL is superior to the SSRIs in helping patients reach remission' implied that Efexor XL had greater antidepressant efficacy than every SSRI. This had not been shown to be the case. The Panel considered that the claim was exaggerated and did not reflect the data accurately. Breaches of the Code were ruled. Upon appeal by Wyeth, the Appeal Board upheld the Panel's rulings.

With regard to the claims 'Well tolerated Placebo levels of tolerability by week 1' (detail aid) and 'Tolerability right from the start' (leavepiece), Lundbeck noted that the Efexor XL summary of product characteristics (SPC) listed a number of adverse events which occurred at a higher frequency with Efexor XL compared to placebo. Tolerability should also be judged not only by the presence or absence of nausea but by various factors including withdrawal from studies due to adverse events;

withdrawal data from Thase *et al* and Cunningham *et al* (1997) were discussed. Lundbeck alleged that the claim for tolerability appeared to be at variance with the Efexor XL SPC and published data.

Lundbeck stated that the claim 'Tolerability right from the start' in the leavepiece was contradicted later in the same piece by the claim 'The incidence of nausea with Efexor XL was no greater than placebo from week one', even, if indeed, one could explain tolerability with nausea alone. The suggestion was therefore of 'good tolerability' from the start, which again was misleading.

The Panel noted that the claim 'Well tolerated Placebo levels of tolerability by week 1' appeared as a heading to a page of the detail aid which featured a graph which depicted the incidence of nausea in patients receiving Efexor XL (75mg/day) or paroxetine (20mg/day) relative to placebo. By week one the incidence of nausea in Efexor-treated patients dropped from +7% compared to placebo to +2% and remained more or less at that level for the next seven weeks. Conversely the incidence of nausea in paroxetine-treated patients remained more than 9% greater than that observed with placebo for the whole of the study. A claim below the graph stated 'The incidence of nausea with Efexor XL 75mg was similar to that of the placebo group after week 1'.

The leavepiece in question was concerned principally with the potential of Efexor to interact with other medicines. The first of two bullet points read 'Tolerability right from the start'. A second bullet point followed, together with a table of data relating to possible interactions. A claim below the table of data read 'The incidence of nausea with Efexor XL was no greater than placebo from week one'.

The Efexor XL SPC stated that the most commonly observed adverse events associated with the use of venlafaxine in clinical trials, and which occurred more frequently than those which were associated with placebo, were nausea, insomnia, dry mouth, somnolence, dizziness, constipation, sweating, nervousness, asthenia and abnormal ejaculation/orgasm. The occurrence of most of these adverse events was dose-related, and the majority of them decreased in intensity and frequency over time. They generally did not lead to cessation of treatment.

The Panel considered that the heading to the relevant page of the detail aid 'Well tolerated Placebo levels of tolerability by week 1' was a general claim relating to more than just nausea. The SPC referred to a number of adverse events associated with the use of venlafaxine which occurred more frequently than with placebo. The Panel noted that the SPC stated that the majority of such adverse events decreased in intensity and frequency over time but considered that this was a much more cautious statement than that in the detail aid 'Placebo levels of tolerability by week 1'. The Panel considered that the page heading was inconsistent with the particulars stated in the Efexor XL SPC and was misleading in that regard. The Panel similarly considered that the claim 'Tolerability right from the start' was also inconsistent with the particulars stated in the Efexor XL SPC and so was misleading in that regard. Breaches of the Code were ruled. Upon appeal by Wyeth, the Appeal Board upheld the Panel's rulings.

Lundbeck noted that the claim about interactions in the detail aid 'Efexor XL is well tolerated with minimal potential for drug interactions' was referenced to Ereshefsky and Dugan (2000). Attention was also drawn to the claim 'Minimal potential for drug interactions' which appeared in one of the leavepieces. The claim was alleged to contradict the Efexor XL SPC which described a number of important interactions.

The Panel noted that the Efexor XL SPC contained a number of warnings regarding the concomitant use of venlafaxine with other medicines. The first group of medicines so listed were MAOIs followed by 'other CNS-active drugs'. Some of the interactions listed had serious consequences, whereas others had pharmacokinetic consequences which did not have any clinical impact. It was stated that the risk of using venlafaxine in combination with other CNS-active drugs had not been systematically evaluated, except for the cases described, and so caution was advised if the concomitant use of venlafaxine and other CNS-active medicines was required. The Efexor XL SPC listed concomitant use of venlafaxine and MAOIs as a contraindication. In addition, the SPC listed a number of other medicines with which Efexor might or might not produce a clinically significant interaction. Caution was advised when administering medicines which were eliminated by the same pathways as venlafaxine; such interactions had not been studied to date.

The Panel considered that the claim 'minimal potential for drug interactions' was misleading. It implied that the chance of an interaction occurring was so small that it need not be considered; such an implication was inconsistent with the SPC which urged caution. A breach was ruled. Upon appeal by Wyeth, the Appeal Board upheld the Panel's ruling.

Lundbeck stated that the claim 'Efexor XL relieves residual symptoms more effectively than SSRIs, helping significantly more patients reach remission' in the detail aid did not appear in Thase *et al* to which it was referenced. It was not clear from where the claim about venlafaxine treatment relieving residual symptoms came from. This was alleged to be inaccurate, ambiguous and misleading.

The Panel noted its previous comments about Thase *et al* and considered that the claim implied that Efexor XL had been shown to produce greater remission rates than every SSRI; this was not so. The claim was inaccurate and misleading in this regard. A breach of the Code was ruled. Upon appeal by Wyeth, the Appeal Board upheld the Panel's ruling.

Lundbeck noted that the claim 'All antidepressants are not equal' appeared as a strapline throughout the detail aid and was combined with rosette artwork. Midway through the detail aid a double page spread depicted only a rosette, labelled 1st in its middle,

which suggested that venlafaxine was the first choice. Lundbeck alleged that the juxtaposition of the rosette to the brand name together with the strapline 'All antidepressants are not equal', subtly changing to a '1st' rosette, were designed to show a superiority over all antidepressants which was unsubstantiated and disparaged other treatments.

The Panel noted that the strapline 'All antidepressants are not equal' appeared each time in association with a green rosette and the Efexor XL brand logo. Twice in the detail aid, in the middle on its own and on the front page in association with the statement 'In the fight against depression, it's remission that wins', the rosette appeared with a gold 1st in its centre. On those pages of the detail aid considered above, venlafaxine had been favourably compared with SSRIs in terms of remission rates. The Panel noted its comments and rulings in this regard.

The Panel considered that the combination of the strapline 'All antidepressants are not equal' with a rosette, which in some places had a gold 1st in its centre and was thus associated with winning, implied that Efexor XL was superior compared with all other antidepressants. This had not been shown to be so. The Panel ruled that the strapline and artwork were misleading in that respect and in breach of the Code. Upon appeal by Wyeth, the Appeal Board upheld the Panel's rulings.

The Panel did not consider that the claim disparaged other antidepressants *per se*. No breach was ruled in this regard.

Lundbeck Ltd complained about the promotion of Efexor XL (venlafaxine extended release formulation) by Wyeth Pharmaceuticals. Venlafaxine was a serotonin and noradrenaline reuptake inhibitor (SNRI) indicated for the treatment of depression. The items at issue were a detail aid (ref ZEFE360/0902) and four leavepieces (refs ZEFE452/0203, ZEFE450/0203, ZEFE495/0203 and ZEFE409/0902). Contact between the companies had failed to resolve the issues. Lundbeck supplied Cipramil (citalopram) and Cipralex (escitalopram) both of which were selective serotonin reuptake inhibitors (SSRIs) also for the treatment of depression.

1 Claims 'Start with the best odds of reaching remission Superior efficacy versus SSRIs and antidepressants overall' (detail aid page 10) and 'Efexor XL is superior to the SSRIs in helping patients reach remission' (four leavepieces)

COMPLAINT

Lundbeck noted that the claim in the detail aid was illustrated with a graph and supported by Smith *et al* (2002), and in the leavepieces it was additionally supported by Thase *et al* (2001). Lundbeck alleged that the claims were all embracing and inaccurately supported by the references as the studies failed to include various licensed and widely available treatments for depression (such as, *inter alia*, citalopram, escitalopram, nefazodone and reboxetine). The claim 'Efexor XL is superior to the SSRIs in helping patients reach remission' was all embracing as citalopram and escitalopram (both SSRIs) were not included in the analysis. The absence of citalopram from the analysis was specifically noted by Thase *et al* which included other limitations of the study. Lundbeck was aware that there might not have been the appropriate comparator studies available for analysis but then the claim should be limited and specific to the medicines compared in the analyses. Lundbeck noted that Montgomery *et al* (2002) had compared escitalopram with venlafaxine in depression and demonstrated similar overall efficacy with benefits of escitalopram over venlafaxine in terms of remission.

Lundbeck alleged that the claims breached Clauses 7.2 and 7.10 of the Code.

RESPONSE

Wyeth stated that the claim in the detail aid referred to the results of a large meta-analysis by Smith *et al* published in the peer reviewed journal, The British Journal of Psychiatry. Meta-analyses of randomised controlled trials represented the strongest evidence available, being less susceptible to bias than single studies. When it was published this meta-analysis was one of the largest to look at the efficacy of one antidepressant against 'all others', and thus represented a substantial weight of evidence. The mechanism underlying the greater efficacy of venlafaxine was thought to be its dual action of blocking the reuptake of both noradrenaline and serotonin in the brain.

The statement 'Start with the best odds of reaching remission' was made clear by the subheading 'Superior efficacy versus SSRIs and antidepressants overall'. Both these statements clearly referred to the large bar chart on the same page that presented the key data from Smith *et al* and justified the statements above.

Smith *et al* reviewed 32 randomised studies of venlafaxine versus other antidepressants and in particular looked at the odds of reaching remission. The odds of reaching remission were 36% higher if patients were treated with venlafaxine compared to the overall antidepressant group, and 43% greater when venlafaxine was compared to the SSRIs *per se*, both of which were highly statistically significant. Thus this data substantiated the first statement, as patients initiated on venlafaxine treatment had 'the best odds of reaching remission'. This was quite specific and was not exaggerated.

Wyeth noted Lundbeck's concern that not all antidepressants available in the UK were included in the analysis by Smith *et al* but submitted that there was no difference in efficacy between SSRIs themselves, and (perhaps with the exception of amitriptyline which was included in the Smith analysis), between any of the other antidepressants. Lundbeck had also pointed out that citalopram was not included in this analysis, but in a more recent meta-analysis by Entsuah *et al* (2002), of 31 studies that looked at the efficacy of venlafaxine vs the SSRIs (which included 2 studies of citalopram), the overall result was the same as in Smith *et al*, with venlafaxine being statistically significantly superior to

the SSRIs as a group with a number needed to treat of 14 in both meta-analyses.

Wyeth stated that with regard to escitalopram, there remained insufficient data to assess it, although Wyeth noted in the BMJ (10 May) that the Authority remained unconvinced about claims that escitalopram had superior efficacy over citalopram. Lundbeck had also referred to the now largely discredited study by Montgomery *et al* in which claims were made about benefits of escitalopram over venlafaxine with regards to remission. However, when the primary endpoints of the study (week 8, LOCF data) were looked at, it was clear that venlafaxine was superior (at least numerically) to escitalopram. The remission data referred to by Lundbeck was a very selective look at the data which used observed case data with an arbitrary definition of remission, and was not representative of the overall results. Until further data was forthcoming it would appear that escitalopram was very similar to citalopram, which was very similar to the SSRIs as a whole. This was in contrast to the large evidence base for venlafaxine where it had been shown in four different large meta-analyses (and numerous individual studies) to have superior efficacy to the SSRIs, and also to the overall group of antidepressants in Smith *et al*.

Wyeth considered that the claims 'Start with the best odds of reaching remission', and 'Superior efficacy versus SSRIs and antidepressants overall' were specific, reflected the broad evidence and were not exaggerated.

PANEL RULING

The Panel noted that the claim in the detail aid 'Start with the best odds of reaching remission Superior efficacy versus SSRIs and antidepressants overall' appeared above a bar chart referenced to Smith *et al*. The results depicted in the bar chart were explained by the claims which appeared below it indicating that Efexor-treated patients had 36% better odds of achieving remission than those treated with other antidepressants and 43% better odds compared with SSRI-treated patients.

Smith *et al* was a systematic review of 32 double-blind, randomized trials (n=5562) comparing venlafaxine with alternative antidepressants in the treatment of depression. The studies analysed were comparisons of venlafaxine with tricyclic antidepressants (TCAs) (9 studies; n=1508) (clomipramine, imipramine, dothiepin and amitriptyline), SSRIs (20 studies; n=3989) (fluoxetine, fluvoxamine, paroxetine and sertraline) and other antidepressants (3 studies; n=418) (trazodone and mirtazapine). The Panel noted that venlafaxine had thus not been compared to every possible other antidepressant as suggested by the claim in question. For example, no trials of venlafaxine versus doxepin, a tricyclic antidepressant, or citalopram, an SSRI, or reboxetine had been included. No monoamine-oxidase inhibitors (MAOIs) had been included.

Smith *et al* plotted the pooled remission rates on venlafaxine compared with those observed with the other antidepressants. The results showed an advantage for venlafaxine compared with fluoxetine, paroxetine, sertraline and the SSRIs overall but not compared with fluvoxamine. Compared with the other antidepressants (mirtazapine and trazodone) there was no advantage for venlafaxine and only a slight advantage when compared with the tricyclic antidepressants. When the results from all of the studies were pooled there was an advantage for venlafaxine.

The Panel noted that not all of the medicines with which venlafaxine was compared were equally represented in the Smith *et al* review. For example, of the 20 SSRI studies included in the review 13 were comparisons with fluoxetine (n=2763), 2 comparisons were with fluvoxamine (n=120), 4 were with paroxetine (n=814) and 1 was with sertraline (n=147). The data was thus more compelling that there was an advantage for venlafaxine versus fluoxetine as opposed to the advantage observed versus sertraline. One of the limitations of the study stated by Smith *et al* was that apart from the comparison with fluoxetine, there were insufficient comparisons between venlafaxine and individual SSRIs and other antidepressants to draw strong conclusions with regard to specific comparisons. The authors also considered that further studies were required to determine how generalisable their results were to different settings and whether venlafaxine had increased effectiveness in usual clinical practice.

The Panel considered that the claim at issue 'Start with the best odds of reaching remission Superior efficacy versus SSRIs and antidepressants overall' was a broad, unequivocal claim that Efexor XL had greater antidepressant efficacy than every SSRI and all other antidepressants. The Panel noted the data cited in support of the claim and its comments upon it. The Panel considered that the claim was exaggerated and did not reflect the data accurately. Breaches of Clauses 7.2 and 7.10 were ruled. These rulings were appealed.

The claim in the leavepieces, 'Efexor XL is superior to the SSRIs in helping patients reach remission' was referenced to Smith *et al* and Thase *et al*. Thase *et al* pooled data from 8 comparable, randomized, double-blind studies of major depressive disorder to compare remission rates during treatment with venlafaxine (n=851) or SSRIs (fluoxetine n=591; paroxetine n=85; fluvoxamine n=34). Thase *et al* stated that one of the limitations of the study was that there were not a sufficient number of studies to compare venlafaxine with specific SSRIs other than fluoxetine. The Panel noted that, as in Smith *et al*, no comparisons of venlafaxine with either citalopram or escitalopram had been included. The Panel noted its comments on Smith *et al* above.

The Panel considered that the claim 'Efexor XL is superior to the SSRIs in helping patients reach remission' implied that Efexor XL had greater antidepressant efficacy than every SSRI. This had not been shown to be the case. The Panel considered that the claim was exaggerated and did not reflect the data accurately. Breaches of Clauses 7.2 and 7.10 were ruled. These rulings were appealed.

APPEAL BY WYETH

Wyeth submitted that the claim 'Start with the best odds of reaching remission' was primarily derived from Figure 1 in Smith *et al* which was a 'Forest plot' of the remission rates showing the individual medicines, the pool of the medicine classes, and the 'overall pooled' result at the bottom. The pooled SSRI and the 'overall pooled' were statistically significantly in favour of venlafaxine, from which the claim, and its qualifying statements 'Superior efficacy versus SSRIs and antidepressants overall' were derived. Thus the claim and qualifying statements accurately represented the data in the paper.

Wyeth accepted that a valid point was made that not all the SSRIs were included in this meta-analysis, and some of the SSRIs had more studies than others, which made the results of some of the SSRIs more robust. For example there were more studies with fluoxetine and paroxetine, and the pool of these individual SSRIs demonstrated that venlafaxine had superior efficacy over each of them individually. There was only one study of sertraline (which reached statistical significance in favour of venlafaxine), and there was one study of fluvoxamine which had a total of only 28 patients which had not reached statistical significance at all. In this meta-analysis there were no studies of citalopram or escitalopram and the question had been raised of whether venlafaxine might have greater efficacy over these compounds.

Wyeth noted that all the SSRIs worked in a similar way by blocking the reuptake of serotonin in the brain. At standard dosing this reuptake was 100% inhibited, which was why the SSRIs did not have a dose-response (Preskorn, 1997). From the pharmacology alone one would not anticipate that different SSRIs would have different efficacy, and indeed this seemed to be borne out in practice as demonstrated by a large meta-analysis of 10,706 patients on SSRIs from over one hundred studies which confirmed that there was no difference in efficacy between any of the SSRIs (Anderson, 2000). This study included 6 studies on citalopram which, if anything, was the least effective of all the SSRIs.

Wyeth submitted that as escitalopram was a new antidepressant there was a relative paucity of data. It was clear from the Panel's ruling that there was still a large question mark as to whether it was superior to citalopram and in this regard Wyeth referred to an article by Dyer, 2003. Montgomery *et al*, which was widely distributed by Lundbeck was flawed on many fronts. One of the main problems was that the study was designed as a 'non-inferiority' study, which, according to the FDA, was not a suitable design in an area such as depression where up to 50% of the studies were 'null' (ie the antidepressant failed to separate from placebo). Furthermore the confidence intervals were set at 90% (rather than the more usual 95%) and observed case analysis was used throughout. To suggest, from one flawed study, that escitalopram was as efficacious as venlafaxine was premature.

In summary, the evidence both from pharmacology and efficacy, suggested that all the SSRIs had similar efficacy and that venlafaxine had superior efficacy to the SSRIs. This was further supported by a very large meta-analysis (Entsuah *et al*) of 32 studies of SSRIs (including citalopram) vs venlafaxine, which demonstrated higher remission rates with venlafaxine that the SSRIs. Thus Smith *et al* was representative of the overall data on venlafaxine and the SSRIs, and to state that venlafaxine had superior efficacy to the SSRIs both reflected that data accurately and was not exaggerated.

Wyeth agreed that venlafaxine had not shown a statistical advantage versus mirtazapine. Accepting that there was only one study, which was reflected in 95% confidence intervals, which passed equivalence, no difference was seen between venlafaxine and mirtazapine. Thus one could choose either medicine to 'start with the best odds of reaching remission'. However, when all the antidepressants were pooled, then there was a clear advantage for venlafaxine, and this was what was represented in the graphs both in Smith *et al* and the detail aid.

Wyeth in summary, submitted that the claim 'Start with the best odds of reaching remission', qualified with 'Superior efficacy versus SSRIs and antidepressants overall' was quite specific, represented the available data, reflected the data accurately and was within the normal school of thought, and, as such did not breach Clauses 7.2 and 7.10.

COMMENTS FROM LUNDBECK

Lundbeck stated that following review of the Panel's ruling and Wyeth's appeal it considered that the Panel had been very thorough in its considerations and it had nothing further to add.

APPEAL BOARD RULING

The Appeal Board noted that the claim in the detail aid 'Start with the best odds of reaching remission Superior efficacy versus SSRIs and antidepressants overall' appeared above a bar chart referenced to Smith *et al*. The data presented in the bar chart were explained by claims below which indicated that Efexor-treated patients had 36% better odds of achieving remission than those treated with other antidepressants and 43% better odds compared with SSRI-treated patients.

The Appeal Board noted from Smith *et al* that venlafaxine had not been compared to every possible other antidepressant as suggested by the claim in question. One of the limitations of the study stated by Smith *et al* was that there were insufficient comparisons between venlafaxine and individual SSRIs and other antidepressants to draw strong conclusions with regard to specific comparisons. The authors also considered that further studies were required to determine how generalisable their results were to different settings and whether venlafaxine had increased effectiveness in usual clinical practice.

The Appeal Board also noted that not all of the medicines with which venlafaxine was compared were equally represented in the Smith *et al* review as conceded by Smith. The Appeal Board considered that the claim at issue 'Start with the best odds of reaching remission Superior efficacy versus SSRIs and

antidepressants overall' was a broad, unequivocal claim which implied that Efexor had greater antidepressant efficacy than every SSRI and all other antidepressants. The Appeal Board considered that, with regard to the SSRIs, the claim was extrapolating data and implying a class effect that had not been proven. This was not acceptable. The Appeal Board considered that the claim was exaggerated and was not a fair reflection of the data. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.10. The appeal on this point was unsuccessful.

The claim in the leavepieces, 'Efexor XL is superior to the SSRIs in helping patients reach remission' was referenced to Smith *et al* and Thase *et al*. The Appeal Board noted that Thase *et al* had not included comparisons of venlafaxine with either citalopram or escitalopram. The Appeal Board noted its comments on Smith *et al* above.

The Appeal Board considered that the claim 'Efexor XL is superior to the SSRIs in helping patients reach remission' implied that Efexor XL had greater antidepressant efficacy than every SSRI. This had not been shown to be the case. The Appeal Board considered that the claim was exaggerated and did not reflect the data accurately. The Appeal Board upheld the Panel's ruling of breaches of Clauses 7.2 and 7.10. The appeal on this point was unsuccessful.

2 Claims 'Well tolerated Placebo levels of tolerability by week 1' (detail aid page 6) and 'Tolerability right from the start' (leavepiece ZEFE409/0902)

COMPLAINT

Lundbeck noted that the Efexor XL summary of product characteristics (SPC) listed a number of adverse events which occurred at a higher frequency with venlafaxine XL compared to placebo (nausea, insomnia, dry mouth, somnolence, dizziness, constipation, sweating, nervousness, asthenia and abnormal ejaculation / orgasm). Tolerability should also be judged not only by the presence or absence of nausea but by various factors including withdrawal from studies due to adverse events. Thase *et al* stated 9% of patients were withdrawn from venlafaxine therapy because of side effects compared to 2% of placebo treated patients (Fisher's exact test p=0.001). Similarly Cunningham *et al* (1997), in a placebo controlled comparison of venlafaxine immediate release (IR) vs venlafaxine XL, reported that adverse events were the primary reasons for premature discontinuation with rates for placebo (2%) less than either venlafaxine preparation (XL 11%, IR 13%). Asthenia, dizziness, insomnia, nausea and nervousness were the most common adverse events causing discontinuation. Nausea was the most common adverse event (placebo 10% vs venlafaxine XL 45%).

Lundbeck alleged that the claim for tolerability appeared to be at variance with the Efexor XL SPC and published data, in breach of Clause 7.2 of the Code.

The claim 'Tolerability right from the start' in the leavepiece was contradicted later in the same piece by the claim 'The incidence of nausea with Efexor XL was no greater than placebo from week one', even, if indeed, one could explain tolerability with nausea alone. The suggestion was therefore of 'good tolerability' (it was unlikely that the statement referred to poor tolerability) from the start, which again was misleading. Lundbeck alleged that these statements and their contradictory nature were similarly in breach of Clause 7.2 of the Code.

RESPONSE

Wyeth stated that the claim in the detail aid referred to the graph that appeared under it showing that the incidence of nausea with venlafaxine returned to placebo levels after one week (Salinas 1997). Nausea was chosen because it was the commonest side effect seen with venlafaxine and the SSRIs.

Wyeth stated that there was no claim or suggestion that other adverse effects did not occur, and agreed that events such as headaches, dizziness and sweating did sometimes manifest themselves in patients taking venlafaxine, as they did with the SSRIs, and that sometimes these led patients to withdraw from therapy.

Lundbeck was correct in stating that in Thase *et al* 9% of patients dropped out due to adverse events on venlafaxine and that 7% dropped out due to adverse events on SSRIs. This was not statistically different. The SSRIs were considered to be 'well tolerated', especially in comparison to the older TCAs, and thus venlafaxine would be considered well tolerated in this context. In Smith *et al* dropout rates due to adverse events were also not statistically different when compared to the SSRIs. When the newer formulation of venlafaxine (the once daily XL capsule) was compared to the SSRIs, there were fewer dropouts (p=ns) due to adverse events in the venlafaxine group compared to the SSRIs (and statistically significantly fewer dropouts due to adverse events on venlafaxine compared to the TCAs) (Einarson *et al* 1999).

Thus venlafaxine had similar tolerability to the SSRIs which were considered to be well tolerated, and it therefore seemed reasonable to state that venlafaxine was well tolerated. The most common adverse event was nausea, which was usually transient and reached placebo levels by the end of the first week.

Wyeth considered that the claim in the detail aid was therefore balanced and reflected the broad body of evidence.

Regarding the claim in the leavepiece 'Tolerability right from the start', this was intended as a general statement referring to the incidence of nausea and the minimal potential of drug interactions as laid out in the leavepiece. As the tolerability was very similar to the SSRIs (see above), Wyeth submitted that the statement was entirely justified.

PANEL RULING

The Panel noted that the claim 'Well tolerated Placebo levels of tolerability by week 1' appeared as a heading to page 6 of the detail aid. The page itself featured a graph adapted from Salinas which depicted the

incidence of nausea in patients receiving Efexor XL therapy (75mg/day) or paroxetine (20mg/day) relative to placebo. The results showed that by week one the incidence of nausea in Efexor-treated patients dropped from +7% compared to placebo to +2% and remained more or less at that level for the next seven weeks. Conversely the incidence of nausea in paroxetine-treated patients remained more than 9% greater than that observed with placebo for the whole of the study. A claim below the graph stated 'The incidence of nausea with Efexor XL 75mg was similar to that of the placebo group after week 1'.

The leavepiece in question was concerned principally with the potential of Efexor to interact with other medicines. The first of two bullet points read 'Tolerability right from the start'. A second bullet point followed, together with a table of data relating to possible interactions. A claim below the table of data read 'The incidence of nausea with Efexor XL was no greater than placebo from week one'.

The Efexor XL SPC stated in Section 4.8, Undesirable Effects, that the most commonly observed adverse events associated with the use of venlafaxine in clinical trials, and which occurred more frequently than those which were associated with placebo, were nausea, insomnia, dry mouth, somnolence, dizziness, constipation, sweating, nervousness, asthenia and abnormal ejaculation/orgasm. The occurrence of most of these adverse events was dose-related, and the majority of them decreased in intensity and frequency over time. They generally did not lead to cessation of treatment.

The Panel considered that the heading to page 6 of the detail aid 'Well tolerated Placebo levels of tolerability by week 1' was a general claim relating to more than just nausea. The SPC referred to a number of adverse events associated with the use of venlafaxine which occurred more frequently than with placebo. The Panel noted that the SPC stated that the majority of such adverse events decreased in intensity and frequency over time but considered that this was a much more cautious statement than that in the detail aid 'Placebo levels of tolerability by week 1'. The Panel considered that the page heading was inconsistent with the particulars stated in the Efexor XL SPC and was misleading in that regard. A breach of Clause 7.2 was ruled. This ruling was appealed.

The claim 'Tolerability right from the start' appeared as the first claim on a leavepiece. The Panel noted its comments above regarding the SPC and the decrease in intensity and frequency of side-effects over time. The Panel considered that the statement in the SPC was more cautious than the claim 'Tolerability right from the start'. The Panel considered that the claim was inconsistent with the particulars stated in the Efexor XL SPC and so was misleading in that regard. A breach of Clause 7.2 was ruled. This ruling was appealed.

APPEAL BY WYETH

Wyeth submitted that the Panel's main concern appeared to be that the company was 'mixing and matching' the two claims above, which was not the case. The first claim was referring to the levels of nausea demonstrated by the large graph in the detail aid positioned under the heading. The second claim (from the leavepiece) was a more general statement about the overall tolerability of venlaflaxine which was on a par with the SSRIs. This could be backed up from the Smith meta-analysis in which dropout rates due to adverse events were non-statistically different when compared with the SSRIs. When the newer formulation of venlafaxine (the once-daily XL capsule) was compared to the SSRIs there were fewer dropouts (non-statistical significance) due to adverse events in the venlafaxine group compared to the SSRIs, and statistically significantly fewer dropouts due to adverse events with venlafaxine compared to the TCAs (Einarson *et al*).

Wyeth submitted that venlafaxine had similar tolerability to the SSRIs which were themselves considered to be well tolerated, and it therefore seemed reasonable to state that venlafaxine was well tolerated itself 'right from the start'. The most common adverse event was nausea, which was usually transient, and reached placebo levels by the end of the first week. No medicine was without side effects, but the data suggested that venlafaxine was as well tolerated as the SSRIs and thus would be considered to have 'tolerability right from the start'.

COMMENTS FROM LUNDBECK

As in point 1 above, Lundbeck stated that it had nothing further to add.

APPEAL BOARD RULING

The Appeal Board considered that the heading to page 6 of the detail aid 'Well tolerated Placebo levels of tolerability by week 1' was a general claim that could be read as referring to a broad safety profile and not just nausea as the graph below depicted. The SPC referred to a number of adverse events associated with the use of venlafaxine which occurred more frequently than with placebo and stated that the majority of such adverse events decreased in intensity and frequency over time. The Appeal Board considered that the SPC was much more cautious than 'Placebo levels of tolerability by week 1'. The Appeal Board considered that the page heading was inconsistent with the particulars stated in the Efexor XL SPC and was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

The claim 'Tolerability right from the start' appeared as the first claim on a leavepiece. The Appeal Board noted however that nausea was a common side effect at the beginning of therapy. The Appeal Board considered that the SPC was more cautious than the claim 'Tolerability right from the start'. The Appeal Board considered that the claim was inconsistent with the particulars stated in the Efexor XL SPC and so was misleading in that regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

3 Claims 'Efexor XL is well tolerated with minimal potential for drug interactions' (detail aid page 7 and leavepieces ZEFE452/0203 and ZEFE450/0203) and **'Minimal potential for drug interactions'** (leavepiece ZEFE409/0902)

COMPLAINT

Lundbeck noted that the claim about interactions in the detail aid was referenced to Ereshefsky and Dugan (2000). This claim contradicted the Efexor XL SPC that specifically described a number of important interactions, including an explicit warning about the interaction between venlafaxine and the MAOIs. The SPC also stated 'The risk of using venlafaxine in combination with other CNS [central nervous system]-active drugs has not been systematically evaluated…', and further that 'the major elimination pathways for venlafaxine are through CYP2D6 and CYP3A4. Therefore, caution should be used with concomitant intake of drugs that inhibit both of these enzymes. Such interactions have not been studied to date'. CYP2D6 inhibitors included amiodarone and quinidine, and CYP3A4 inhibitors included cimetidine, clarithromycin, erythromycin, grapefruit juice and ketoconazole that were all well used compounds. The SPC also contained the warning that: 'Potentiation of anticoagulant effects including increases in [prothrombin time] or [international normalized ratio] have been reported in patients taking warfarin following the addition of venlafaxine'.

Lundbeck alleged that the claims were at variance with the Efexor XL SPC in breach of Clause 7.2 of the Code.

RESPONSE

Wyeth stated that the issue here was whether venlafaxine was likely to interact with the metabolism of other medicines. The key cytochrome P450 enzymes (liver enzymes) that were involved with drug metabolism were CYP2D6, CYP1A2 and CYP3A4. Venlafaxine was a relatively weak inhibitor of CYP2D6 and did not inhibit CYP1A2 or CYP3A4.

The specific interaction with MAOIs (another class of antidepressant) was a very well known interaction, and occurred because both medicines acted on the same receptors in the brain. If MAOIs and other antidepressants were dosed together it could lead to serious complications, and as such the concomitant use of an MAOI with venlafaxine was contra-indicated, as stated in the SPC and prescribing information. This would be the same for SSRIs. The interaction was not due to inhibition or increased metabolism of either medicine and it was not considered a 'usual' drug interaction. In fact it was quite common practice not to include this specific interaction under drug interactions; Wyeth noted that a Lundbeck leavepiece on Cipramil (0201/CIP/525/341(596)) referred to 'low risk of drug interactions', at the same time contra-indicating the concurrent use of MAOIs in its prescribing information.

Wyeth noted that in the detail aid it cited Ereshefsky and Dugan, a review of the potential for venlafaxine to interact with other drugs. The authors concluded 'Patients who are treated with venlafaxine, compared to patients treated with SSRIs or [tricyclic antidepressants], probably have a lower risk for drug-drug interactions, which is an important consideration in patients who are elderly or disabled, who have hepatic disease, and who take multiple medications'.

Wyeth thus considered that the claim that venlafaxine had a minimal potential for drug interactions was fully substantiated.

PANEL RULING

The Panel noted that Section 4.5 of the Efexor XL SPC, Interactions with Other Medicaments and Other Forms of Interaction, contained a number of warnings regarding the concomitant use of venlafaxine with other medicines. The first group of medicines so listed were MAOIs followed by 'other CNS-active drugs'. Some of the interactions listed had serious consequences eg venlafaxine and MAOIs, whereas others had pharmacokinetic consequences which did not have any clinical impact eg venlafaxine and risperidone. It was stated that the risk of using venlafaxine in combination with other CNS-active drugs had not been systematically evaluated, except for the cases described, and so caution was advised if the concomitant use of venlafaxine and other CNS-active medicines was required. The Panel noted that Section 4.3 of the Efexor XL SPC listed concomitant use of venlafaxine and MAOIs as a contraindication.

In addition to the above, the SPC listed a number of other medicines with which Efexor might interact. Again, in some cases such interactions could be clinically important eg venlafaxine with cimetidine in the elderly or those with hepatic dysfunction, whereas in others the clinical significance of a pharmacokinetic interaction was not known eg concomitant use of venlafaxine and indinavir. Caution was advised when administering medicines which were eliminated by the same pathways as venlafaxine; such interactions had not been studied to date.

The Panel considered that the claim 'minimal potential for drug interactions' was misleading. It implied that the chance of an interaction occurring was so small that it need not be considered; such an implication was inconsistent with the SPC which urged caution. A breach of Clause 7.2 was ruled. This ruling was appealed.

APPEAL BY WYETH

Wyeth submitted that the primary issue was whether venlafaxine was likely to interact with the metabolism of other medicines. The key cytochrome P450 enzymes (liver enzymes) that were involved with the metabolism of medicines were CYP2D6, CYP1A2 and CYP3A4. Venlafaxine was a relatively weak inhibitor of CYP2D6 and did not inhibit the other two (Efexor SPC). Thus venlafaxine was unlikely to interact with other medicines via this mechanism.

The second point was whether other medicines interacted with venlafaxine. As venlafaxine was metabolised via two pathways (via CYP2D6 and CYP3A4), and both venlafaxine *per se* and the

metabolite (O-Desmethyl venlafaxine (ODV)) were active compounds, interactions of this sort would be extremely unlikely. If both cytochromes were inhibited the higher levels of venlafaxine would be offset by the lower levels of ODV, and the converse would happen in a fast metaboliser. As both compounds were active the net effect remained the same. If just one iso-enzyme was inhibited, the overall effect would be minimal, as the other would compensate. So medicine interactions of this sort were also unlikely.

Wyeth submitted that for these reasons it considered the claim 'Minimal potential for drug interactions' to be entirely justified. One could argue that if this statement could not be made for venlafaxine, then it should not be made for any antidepressant.

Wyeth submitted that the specific interaction with MAOIs (another type of antidepressant) was very well known and occurred because both medicines acted on the same receptors in the brain. If MAOIs and other antidepressants were dosed together it could lead to serious complications, and as such the concomitant use of an MAOI with venlafaxine was contra-indicated as stated in the SPC and prescribing information. This would be the same for SSRIs, and as stated previously, Lundbeck in its own promotional leavepiece (0201/CIP/525/341(596)) referred to 'low risk of drug interactions', at the same time contraindicating the concurrent use of MAOIs in its prescribing information. The list of specific medicine interactions in Section 4.5 in the SPC was generally reassuring, with the majority showing no interaction. Wyeth submitted that it was important to show these as they might be used concurrently with venlafaxine. The most common potential concomitant medicines (alcohol, lithium, diazepam) showed no interactions, which was of reassurance. There was a general statement about using other CNS drugs at the same time as venlafaxine, but this was more about common sense than any specific warning, and as stated above the most commonly used medicines had been studied individually for interactions. The protein binding of venlafaxine was low, and thus these types of medicine interactions were also unlikely to occur.

Wyeth thus considered that the claim that venlafaxine had a minimal potential for drug interactions was fully substantiated.

COMMENTS FROM LUNDBECK

As in point 1 above, Lundbeck stated that it had nothing further to add.

APPEAL BOARD RULING

The Appeal Board noted that the Efexor XL SPC referred to a number of medicines with which venlafaxine might interact. There was thus the potential for interaction with other medicines.

In the Appeal Board's view however, use of the word minimal implied that the risk of such interaction was so small that it need not be considered. The Appeal Board considered that the claim 'Minimal potential for drug interactions' was not a fair reflection of the SPC and was misleading in this regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

4 Claim 'Efexor XL relieves residual symptoms more effectively than SSRIs, helping significantly more patients reach remission'

This claim appeared on page three of the detail aid and was referenced to Thase *et al*. The page was headed 'Helps more patients reach remission Remission at week 8' and featured a bar chart depicting the results of Thase *et al*. The bar chart showed that 25%, 35% and 45% of patients achieved remission on placebo, SSRIs and Efexor XL respectively.

COMPLAINT

Lundbeck stated that nowhere in Thase *et al* did the claim exist and that it was not clear from where the claim about venlafaxine treatment relieving residual symptoms came from. This was therefore inaccurate, ambiguous, and misleading in breach of Clause 7.2 of the Code.

RESPONSE

Wyeth stated that this page of the detail aid demonstrated the data from one of the meta-analyses that consistently showed the superior efficacy of venlafaxine over the SSRIs. In Thase *et al*, the key end point of remission was shown for placebo, SSRIs and venlafaxine. It was quite clear from the bar chart that 45% of patients on venlafaxine attained remission, compared to 35% of patients on SSRIs ($p<0.001$). Thus it was clear that venlafaxine helped more patients reach remission than the SSRIs. This result was consistent with Smith *et al*, Einarson *et al* (1999) and Entsuah *et al* (2002), and reflected current thinking. In order to reach remission, residual symptoms (symptoms of depression that were still present after treatment with an antidepressant) had to be eliminated, and as more patients attained remission with venlafaxine, it was clear that 'Efexor XL relieves residual symptoms more effectively than SSRIs'.

Wyeth considered the claim was an accurate reflection of the evidence and was not inaccurate, ambiguous or misleading.

PANEL RULING

The Panel noted that the claim 'Efexor XL relieves residual symptoms more effectively than SSRIs, helping significantly more patients reach remission' was referenced to Thase *et al*. Thase *et al* pooled data from 8 comparable, randomized, double-blind studies of major depressive order to compare remission rates during treatment with venlafaxine (n=851) or SSRIs (fluoxetine n = 591; paroxetine n = 85; fluvoxamine n = 34). Thase *et al* stated that one of the limitations of the study was that there was not a sufficient number of studies to compare venlafaxine with specific SSRIs other than fluoxetine. The Panel noted that no comparisons with escitalopram had been included either in Thase *et al* or in any of the three other studies cited by Wyeth in its response ie Smith *et al*, Einarson *et al* and Entsuah *et al*.

The Panel considered that the claim implied that Efexor XL had been shown to produce greater remission rates than every SSRI; this was not so. The claim was inaccurate and misleading in this regard. A breach of Clause 7.2 was ruled. This ruling was appealed.

APPEAL BY WYETH

Wyeth referred to its submission at point 1 above.

Wyeth submitted that this page of the detail aid demonstrated the data from Thase *et al*, one of the meta-analyses that consistently showed the superior efficacy of venlafaxine over the SSRIs. The key end point of remission was shown for placebo, SSRIs and venlafaxine. It was quite clear from the graph that 45% of patients on venlafaxine attained remission, compared to 35% of patients on SSRIs, a statistically significant result. Thus it was clear that venlafaxine helped more patients reach remission than the SSRIs as shown in the graph. This result was consistent with the meta-analyses by Smith *et al*, Einarson *et al* and Entsuah *et al*, and reflected current thinking. In order to reach remission, residual symptoms (symptoms of depression that were still present after treatment with an antidepressant) had to be eliminated, and as more patients attained remission with venlafaxine it was clear that 'Efexor XL relieves residual symptoms more effectively than SSRIs'.

COMMENTS FROM LUNDBECK

As in point 1 above, Lundbeck stated that it had nothing further to add.

APPEAL BOARD RULING

The Appeal Board noted that the claim at issue was referenced to Thase *et al*. One of the limitations of that study was that there was not a sufficient number of studies to compare venlafaxine with specific SSRIs other than fluoxetine. The Appeal Board noted that no comparisons with escitalopram had been included and that any patients who had previously not responded to SSRI therapy had not been excluded. In addition the studies included in the meta-analysis had lasted for only 6 or 8 weeks. There was thus no long-term data. Thus the advantage shown for venlafaxine vs the SSRIs could have been due to the inclusion of patients who had previously failed to respond to SSRIs.

The Appeal Board considered that the data from Thase *et al* was of insufficient duration to support such a bold claim. In addition the claim implied that Efexor XL had been shown to produce greater remission rates than every SSRI; this was not so. The claim was inaccurate and misleading in this regard. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.2. The appeal on this point was unsuccessful.

5 Claim 'All antidepressants are not equal'

Lundbeck stated that the claim appeared as a strapline throughout the detail aid.

COMPLAINT

Lundbeck noted that this claim was combined with rosette artwork. Midway through the detail aid a double page spread depicted only a rosette, labelled 1st in its middle (pages 8 and 9) which suggested that venlafaxine was the first choice. Initially the rosette appeared on the cover with a strapline 'In the fight against depression, it's remission that wins'. On the next six pages the rosette (blank in the middle) appeared alongside the brand name Efexor XL, and was accompanied by the strapline 'All antidepressants are not equal'. There was then a double page spread that carried the large rosette with a 1st written in gold, and the subsequent six pages again showed the blank rosette together with the brand name and strapline 'All antidepressants are not equal'. The artwork of the juxtaposition of the rosette to the brand name together with the strapline 'All antidepressants are not equal', subtly changing to the '1st' rosette were designed to show a superiority over all antidepressants which was unsubstantiated and also disparaged other treatments indirectly.

Lundbeck alleged the artwork to be in breach of Clauses 7.8, 7.2 and 8.1 of the Code.

RESPONSE

Wyeth stated that the main thrust of the detail aid was to highlight the importance of remission, and this was made quite clear on the first page where the statement 'In the fight against depression, it's remission that wins' was accompanied by a rosette with a 1st on it. This represented the idea of 'winning' and the concept that remission should be the primary goal of antidepressant treatment.

Later in the detail aid the strapline 'All antidepressants are not equal' was intended to emphasise the fact that there were differences between antidepressants (which could take the form of efficacy, tolerability or side effect profile). For example, if sleep was an important consideration then a sedating antidepressant such as a TCA or mirtazapine might be appropriate, whereas if efficacy were of prime concern, then venlafaxine might be an appropriate choice. It was self evident, that with all their different characteristics, 'All antidepressants are not equal', and in fact this was a direct quote from the discussion of Smith *et al*. By stating that all antidepressants were not equal, Wyeth was not trying to be disparaging in any way, but just stating that antidepressants had differences.

Wyeth noted that it did not state anywhere in the detail aid that 'venlafaxine was the first choice' as asserted by Lundbeck. Wyeth had presented data to show that venlafaxine was more efficacious than the SSRIs, but fully realised that more than efficacy would determine the appropriate antidepressant for the individual patient.

Wyeth denied that the strapline or artwork were in breach of the Code.

PANEL RULING

The Panel noted that the strapline 'All antidepressants are not equal' appeared each time in association with

a green rosette and the Efexor XL brand logo. Twice in the detail aid, in the middle on its own (pages 8 and 9) and on the front page in association with the statement 'In the fight against depression, it's remission that wins', the rosette appeared with a gold 1st in its centre. On those pages of the detail aid considered at points 1 and 4 above, venlafaxine had been favourably compared with SSRIs in terms of remission rates. The Panel noted its comments and rulings in points 1 and 4.

The Panel considered that the combination of the strapline 'All antidepressants are not equal' with a rosette, which in some places had a gold 1st in its centre and was thus associated with winning, implied that Efexor XL was superior compared with all other antidepressants. This had not been shown to be so. The Panel considered that the strapline and artwork were misleading in that respect and breaches of Clauses 7.2 and 7.8 were ruled. These rulings were appealed.

The Panel did not consider that the claim disparaged other antidepressants *per se*. No breach of Clause 8.1 was ruled.

APPEAL BY WYETH

Wyeth submitted that purpose of the detail aid was to promote the importance of remission, and then to show that venlafaxine was a very useful medicine in helping patients attain remission. Thus there was a rosette on the front page with a '1st' in the centre to emphasise the importance of remission. The accompanying text on the front page was 'In the fight against depression, it's remission that wins' to make the point about the importance of remission. Then later on in the detail aid there was the strapline 'All antidepressants are not equal' which was adjacent to a smaller version of the rosette without the '1st' which was deliberately omitted to be consistent with the Code.

Wyeth submitted that there were different ways of achieving remission, and different antidepressants would suit individual patients, and this was the point that it was trying to make by stating 'All antidepressants are not equal'.

Thus Wyeth denied that the strapline in conjunction with the artwork contravened Clauses 7.2 and 7.8.

COMMENTS FROM LUNDBECK

As in point 1 above, Lundbeck stated that it had nothing further to add.

APPEAL BOARD RULING

The Appeal Board considered that the combination of the strapline 'All antidepressants are not equal' with a rosette, which in some places had a gold 1st in its centre, and was thus associated with winning, implied that Efexor XL was superior compared with all other antidepressants. The Appeal Board considered that the rosette with a gold centre 1st on pages 8 and 9 could be interpreted as providing a conclusion to the data presented on the preceding pages, ie that Efexor XL was superior. This had not been shown to be so. The Appeal Board considered that the strapline and artwork were misleading in that respect and upheld the Panel's rulings of breaches of Clauses 7.2 and 7.8. The appeal on this point was unsuccessful.

Complaint received **6 May 2003**

Case completed **27 June 2003**

CASE AUTH/1463/5/03

SCHWARZ PHARMA/DIRECTOR v NORGINE

Breach of undertaking

Schwarz Pharma complained that a detail aid and a price reduction letter for Movicol (macrogol plus electrolytes), which were available on Norgine's stand at a Journal of Community Nursing (JCN) meeting in April 2003, had been found to contain numerous breaches of the Code in a previous complaint (Case AUTH/1359/9/02); their availability at the meeting constituted a breach of undertaking. As the complaint involved an alleged breach of undertaking it was taken up by the director as it was the responsibility of the Authority itself to ensure compliance with undertakings. This accorded with advice previously given by the Appeal Board.

The Panel noted Norgine's response; the two representatives at the meeting were sure that the materials were not available at their stand. The requisition form for items to be used at JCN meetings did not include either item. One representative had never requested a copy of the price reduction letter. The other representative had never seen a copy of it.

The parties' accounts differed. It was difficult in such circumstances to determine where the truth lay. It was not possible to determine whether the materials had been available on the stand. The Panel was thus obliged to rule no breaches of the Code. The ruling of no breach of the previous undertaking was appealed by Schwarz.

The Appeal Board noted that the Schwarz representative who claimed to have taken items from the Norgine stand stated that she did so as part of her normal practice of 'intelligence gathering'. She had taken a number of different materials from the various stands, some of which she had used for personal education and interest; she had forwarded the Norgine material to head office. The representative had not known that the detail aid she had collected from the Norgine stand had previously been ruled to be in breach of the Code. A copy of an email from the representative's manager stated that the materials which she had sent in to head office had been taken from Norgine's stand at the JCN meeting in question.

The Appeal Board noted that Norgine had been asked by the Authority to provide full details of the steps it had taken to comply with the undertaking given in Case AUTH/1359/9/02. At the appeal hearing Norgine explained that in January its representatives had been required to sign and return a form to verify that all the items listed, including the material at issue, had been returned to head office for disposal. Norgine stated that it had not checked its records to see if the two representatives had returned the form although it considered it unlikely that one of the representatives would have received it anyway as, when it was issued, she was so new to the company.

The Appeal Board noted that the Norgine stand had been manned by two representatives. Both had taken material to the exhibition and both had replenished the stand at various times. The Appeal Board heard that the new detail aid, which replaced the one in question, could be differentiated from its predecessor in that it did not feature the prominent claim for a 30% price reduction on its front cover. The Appeal Board also heard that the Norgine representatives had been very busy on their stand.

The Appeal Board noted that the parties' accounts differed. Schwarz stated that its representative had taken the material from Norgine's unmanned stand, Norgine stated that its stand had never been unmanned and in any event the material in question was not available at the meeting. Nonetheless the fact remained that Schwarz had sent a copy of the detail aid to the Authority some months after it should have been withdrawn from use. Having had an opportunity to assess the accounts of the Schwarz representative and one of the Norgine representatives present at the meeting, the Appeal Board was satisfied on a balance of probabilities that the Schwarz representative had indeed taken the material in question at that meeting. The Appeal Board was also satisfied that the material in question had been made available on the stand completely unintentionally. In the circumstances the Appeal Board ruled a breach of the Code. The appeal on this point was successful.

Schwarz Pharma Limited complained about promotional materials for Movicol (macrogol 3350, sodium bicarbonate, sodium chloride, potassium chloride) which were available on Norgine Limited's stand at a Journal of Community Nursing (JCN) meeting in Bradford in April 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 Appeal Board.

COMPLAINT

Schwarz stated that a detail aid for Movicol (ref MO/02/0096) and a price reduction letter (ref MO/01/0081) were available from the Norgine stand at the meeting.

The detail aid in question had been found to contain numerous breaches of the Code in a previous complaint (Case AUTH/1359/9/02). The price reduction letter made claims that were also found in breach in the same case where there was a failure to make it apparent that the claim was derived from pharmacoeconomic data. As such, the availability of these items subsequent to being found in breach constituted a breach of undertaking. A breach of Clause 22 of the Code was alleged.

In addition to Clause 22 which had been cited by the complainant, the Authority asked Norgine to respond in relation Clauses 2 and 9.1 of the Code.

RESPONSE

Norgine stated that it had interviewed the two representatives who were at the meeting. The materials at issue were old materials; the detail aid was last distributed in early September 2002, and the letter was sent out in February 2002.

Norgine stated that both representatives were very experienced. Both representatives gave exactly the same account of which materials were used and they both remembered exactly which materials were on their stand. Norgine noted that the newer representative who had never seen, during her time at Norgine, any items with '30% price reduction' on the cover was adamant that she would have immediately noticed such an item had it been on the stand.

For JCN meetings, Norgine had a standard list of items from which representatives could request whatever they wanted. One of the representatives spontaneously commented that she always ordered a number of items from the list in advance of a meeting as they usually handed out such a large amount of material at these meetings. The list used for JCN meetings was provided and Norgine noted that items MO/01/0081 and MO/02/0096 were not on it.

The senior representative was also sure that she did not have these materials on the stand and was adamant that she had never seen a copy of the price reduction letter. This was not surprising as the price reduction letters were mailed from head office directly and not primarily distributed via Norgine's representatives, although a small number of copies were made available to representatives on request in February 2002. Not all representatives asked for copies and this representative was one that did not. Furthermore, the newer of the representatives joined the company long after these letters had been sent and also had, as stated above, never seen a copy.

Norgine noted that one of the items alleged to have been on the stand was a detail aid (MO/02/0096). Norgine's representatives used detail aids for exactly the purpose for which they were intended, ie, an aid in the face to face detailing of customers. They were not intended as items to give to doctors or nurses and Norgine representatives did not use them in this manner.

Norgine was very impressed by the consistency of the two accounts. Both representatives gave their accounts with clear and unambiguous recollection of what did and did not occur at this meeting. Having interviewed them Norgine considered that it had been given a true account of events.

Schwarz referred to the items being 'available' on the Norgine stand and gave no further detail. It was not clear where the photocopied items provided by Schwarz might have come from. There was no direct allegation that the items came into the possession of Schwarz on that day, only that they were available on the stand. Was it therefore possible that a Schwarz representative might have seen what they mistook to be these items on the stand and that they were not physically obtained from the meeting? This was a possible explanation, as Norgine's representatives knew the Schwarz representatives at the meeting and did not at any time offer them or see them take items from Norgine's stand, although both representatives recall a Schwarz representative briefly looking at the material on the stand. The stand was not left unattended at any time.

Norgine did not know how or when Schwarz obtained these materials (which had not been in current use for some time), but it was very satisfied that it was not from Norgine's stand at the JCN meeting as alleged.

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/1359/9/02 concerned a complaint about the promotion of Movicol by Norgine. Breaches of the Code had been ruled. The promotional items at issue included, *inter alia*, the detail aid at issue in the present case.

Turning to the present case, Case AUTH/1463/5/03, the Panel noted that Schwarz alleged that in addition to the detail aid, the company stand also included a price reduction letter which featured claims that were ruled in breach in the previous case. The Panel noted that the claims in the price reduction letter, albeit similar, were not identical to those at issue in the previous case, Case AUTH/1359/9/02. Some of the claims at issue in the price reduction letter were referenced to data on file N110 whereas similar claims in the detail aid were referenced to Christie *et al* (2002). Presentation of data from Christie *et al* in the detail aid had been criticised in Case AUTH/1359/9/02. Breaches of the Code had been ruled. In the case now before it the Panel had no way of knowing if the data on file N110 was the same as that published by Christie *et al* and if, therefore, the claims in the price reduction letter were similarly flawed.The Panel noted the allegation that Norgine had breached its undertaking given in Case AUTH/1359/9/02 by making the detail aid and price reduction letter available at its stand. The Panel noted Norgine's response; both its representatives were sure that the materials were not available at the stand. The requisition form for items to be used at JCN meetings did not include either item. One representative had been employed by the company in February 2002 when the price reduction letter was used but had never requested a copy of it. The other representative had never seen a copy of the price reduction letter.

The parties' accounts differed. It was difficult in such circumstances to determine where the truth lay. It was not possible to determine whether the materials had been available on the stand. The Panel was thus obliged to rule no breach of Clauses 2, 22 and 9.1 of the Code. The ruling of no breach of Clause 22 was appealed.

APPEAL BY SCHWARZ PHARMA

Schwarz stated that one of its medical representatives who had attended the JCN meeting had obtained a

number of items from the Norgine stand. The items were thus 'available' from that exhibition stand and Schwarz failed to see how Norgine's comment that its representative in any way might have seen items and mistook them for the ones of which copies were made to submit to the Authority could be considered viable. Schwarz representatives would not be expected to know or determine whether a promotional item that might appear on a stand had previously been ruled on by the Panel. The representative acquired the materials and sent them to Head Office.

Schwarz stated that it was very unlikely that any of the Norgine representatives could be expected to recall all visitors to their stand with sufficient clarity to identify one representative and be sufficiently certain that this representative did not take such materials. There were three representatives from Schwarz Pharma at this particular meeting; the one who sent the items to Head Office stated that the stand was unattended at the time the material was taken.

Schwarz stated that it might well have been one of the Norgine representative's standard practice to have 'always ordered a number of items from the list in advance of a meeting as they usually handed out such a large amount of material at these meetings'. This did not guarantee other materials might be, or might not be, available (inadvertently or not) for visitors to take. There was no assurance that the material was not among that distributed to the representative when requested for the meeting. Schwarz did not consider that an assurance on an individual's standard practice was sufficient to negate the possibility that such materials might still have been available. No individual was infallible and it appeared to be naïve to accept this as so. This was compounded by not considering the procedures utilised to withdraw the items following the original ruling in Case AUTH/1359/9/02. Schwarz alleged that a similar argument existed in view of the 'price reduction letter'.

Schwarz alleged that with these points in mind, it was impossible for Norgine to be so absolutely certain the materials at issue were not available from its stand at the JCN meeting. Whatever its position, these items were taken from a Norgine stand at that meeting.

Schwarz stated that the implication of the Panel's ruling challenged the very foundations of self-regulation. The company had exercised a high standard of prudence in ensuring that the material was retrieved at the stated meeting and it had satisfied itself that there was a case to be answered and had not undertaken the submission of this complaint lightly.

Schwarz noted that in previous cases involving alleged breaches of undertaking, as a consequence of materials being available in similar circumstances (eg Case AUTH/1086/10/00 and Case AUTH/1310/4/02), the procedures for ensuring withdrawal of such items previously found in breach were assessed. This did not seem to be the case with the current decision. There did not appear to have been an appropriate review of the procedures implemented for the withdrawal of items found in breach in Case AUTH/1359/9/02. It remained possible, in this context alone, that items that should have been withdrawn were present at the JCN meeting. The corroboration was the fact that the items themselves were retrieved from the meeting by a Schwarz representative.

Schwarz would have expected that the Panel would have required appropriate confirmation that the procedures were in place and operated accordingly at the time of the meeting. By assessing the procedures in Case AUTH/1086/10/00 and Case AUTH/1310/4/02, the companies concerned identified issues that contributed to the circumstances leading to breaches of undertaking. It would be expected that such an outcome facilitated an improvement in their procedures, reducing the possibility of future such occurrences.

Schwarz questioned what was required beyond the word of a stakeholder in this system of self-regulation? Was Schwarz now required to make such submissions with irrefutable confirmatory evidence that such items were present and available to be taken? What was required for such a case to be proven, especially in the face of a denial by respondent? How otherwise did the Panel propose to ensure such situations were regulated? The fact of this case was that the material was acquired and sent to Head Office.

Schwarz alleged that the Panel's ruling gave scope for 'free reign', as denial of materials being retrieved in such circumstances would question the integrity of the complainant. Furthermore, as it stood, there was nothing precluding materials that should have been withdrawn appearing at such meetings in future. The ruling provided no fear of repercussions if companies found themselves with such materials at meetings, or if other companies submitted these materials to the Authority. Self-regulation provided for a degree of 'self-policing' by stakeholders.

Schwarz alleged that the Panel's ruling allowed a company to distribute, inadvertently or not, materials previously found in breach at meetings. It would only be in the interests of the pharmaceutical industry, in the context of self-regulation, to identify materials from such meetings in this context and submit a breach of undertaking to the Authority. Therefore, the precedent set by this ruling was such that companies could expect to provide an assurance only that the material was not available, and this would be sufficient to disprove liability, simultaneously casting aspersions on the integrity of the complainant, who would be acting in good faith.

COMMENTS FROM NORGINE

Norgine submitted that the nature of Schwarz's complaint seemed to have materially changed. Schwarz had originally stated that 'The items were available at a Norgine stand…' whereas in its appeal it had stated that 'A medical representative of Schwarz ….obtained a number of items from the Norgine exhibition stand'.

Norgine stated that its original response was to an extent based on the specific word 'available' which it submitted had a rather different meaning than the

word 'obtained'. In relation to this, Schwarz had introduced some documentary evidence that was new and was not part of the original complaint.

Norgine noted that this evidence consisted of an email from the medical representative in question, to Schwarz's medical adviser dated 1 July 2003. Norgine presumed that this email was included in the evidence submitted for the appeal on the basis that it corroborated the allegation that the material was obtained from the Norgine stand.

This email stated that the representative attended the Norgine stand at around 1pm and acquired and took away a number of items. The email also stated that at that time there was no one at the Norgine stand. A further email from presumably another Schwarz representative, was enclosed as evidence. This email stated that the second Schwarz representative had confirmed that the first representative went to the Norgine stand and collected some material, although as stated in the email, the second representative did not look at the material in question and would clearly not have been in a position to confirm whether they were or were not the items in question.

Norgine noted that the exhibition was open to visitors (ie the district nurses) from 11.30am to 2pm. Around 1pm would therefore be the time of peak activity for all representatives at their respective stands, and would be the time that they would be least likely to leave stands unmanned.

Norgine had again spoken to each representative individually, and they both independently confirmed that they were definitely at the stand at 1pm. They both confirmed that they did not leave the stand until 2pm at the very earliest when the lunch time meeting had finished and the nurses departed, and at that time they took all materials off the stand, and put them out of sight.

Norgine submitted that it was highly improbable under the circumstances that the Norgine stand was left unattended as alleged at around 1pm, during the busiest time of the meeting.

In response to Schwarz's inference that the document listing the items sent to all JCN exhibitions, might have been produced after the event Norgine noted that it operated in a 'paper light' office, and all such lists were kept on one computer, and printed out and sent to the representatives when required. Norgine submitted that it provided evidence of which materials had been sent to the meeting, the list had been given a heading when it was printed. The list itself was certainly not produced after the event and was a standard list produced for JCN meetings.

Norgine noted that in the past, when considering cases of one company's word against another's without further evidence to corroborate either side, there was no way that the Panel could judge which was the correct version, therefore it had consistently ruled no breach of the Code.

There could be an argument that a no breach ruling in this sort of situation was analogous to the verdict of not proven under Scottish law, although of course the Constitution and Procedure of the Authority did not allow for such a ruling.

Norgine alleged that no amount of indignation from Schwarz could change the facts in this case. A representative of Schwarz claimed to have obtained some specific items from a Norgine stand at a meeting. Schwarz believed the account given by its representative. Two representatives from Norgine claimed they did not possess any of the material in question, and the material was not available on the stand. They claimed that no Schwarz employee obtained any material from the stand in any event. Norgine believed the account given by its representatives. There was no supporting evidence to prove which account was correct.

Norgine considered that the Appeal Board had no basis on which to overturn the Panel's ruling.

FURTHER COMMENTS FROM SCHWARZ

Schwarz stated that the complaint had not materially changed. The items in question were available on the stand ie they were available to be obtained. Norgine's evasion of accepting this insinuated that the material was submitted to the Authority from another source as a pre-meditated attempt to have Norgine ruled in breach of an undertaking. Furthermore, basing an entire response on a single word without investigating all potential avenues did not satisfy the requirements to ensure procedures were in place to prevent such breaches of undertakings.

Under such circumstances was Schwarz to accept the written word of Norgine that the document listing items for JCN meetings was not produced after the event? Perhaps Norgine could submit confirmatory evidence rather than Schwarz accepting its written statement? Otherwise, this in itself appeared to represent a disparity between what was accepted as Norgine's word and that which was accepted from Schwarz's perspective.

APPEAL BOARD RULING

The Appeal Board noted that the Schwarz representative who claimed to have taken items from the Norgine stand stated that she did so as part of her normal practice of 'intelligence gathering'. She had taken a number of different materials from the various stands some of which she had used for personal education and interest; she had forwarded the Norgine material to head office. The representative had not known that the detail aid she had collected from the Norgine stand had previously been ruled to be in breach of the Code (Case AUTH/1359/9/02: Reckitt Benckiser Healthcare v Norgine). A copy of an email from the representative's manager stated that the materials which she had sent in to head office had been taken from Norgine's stand at the JCN meeting in question. At the appeal hearing the Senior Product Manager at Schwarz described how her system for handling in-coming mail had ensured that the material sent by the representative had not been mixed up with any other material. The documents received by the Senior Product Manager had been copied and sent to the Authority.

The Appeal Board noted that Norgine had been asked by the Authority to provide full details of the steps it

had taken to comply with the undertaking given in Case AUTH/1359/9/02. At the appeal hearing Norgine explained that representatives had been sent a memorandum on 3 January which required them to sign and return a form to verify that all the items listed had been returned to head office for disposal. This included the material at issue. Norgine stated that it had not checked its records to see if the two representatives had returned the form although it considered it unlikely that one of the representatives would have received the memorandum anyway as, when it was issued, she was so new to the company.

The Appeal Board noted that the Norgine stand had been manned by two representatives. Both had taken material to the exhibition and both had replenished the stand at various times. The Appeal Board heard at the hearing that the new detail aid, which replaced the one in question, could be differentiated from its predecessor in that it did not feature the prominent claim for a 30% price reduction on its front cover. The Appeal Board also heard that the Norgine representatives had been very busy on their stand.

The Appeal Board noted that the parties' accounts differed. Schwarz stated that its representative had taken the material from Norgine's unmanned stand, Norgine stated that its stand had never been unmanned and in any event the material in question was not available at the meeting. Nonetheless the fact remained that Schwarz had sent a copy of the detail aid to the Authority some months after it should have been withdrawn from use. Having had an opportunity to assess the accounts of the Schwarz representative and one of the Norgine representatives present at the meeting, the Appeal Board was satisfied on a balance of probabilities that the Schwarz representative had indeed taken the material in question at that meeting. The Appeal Board was also satisfied that the material in question had been made available on the stand completely unintentionally. In the circumstances the Appeal Board ruled a breach of Clause 22 of the Code. The appeal on this point was thus successful.

Complaint received **12 May 2003**

Case completed **23 September 2003**

CASES AUTH/1468/5/03 and AUTH/1469/5/03

MERCK SHARP & DOHME v PROCTER & GAMBLE and AVENTIS PHARMA

Actonel detail aid

Merck Sharp & Dohme complained about a 12 page detail aid for Actonel (risedronate) which discussed the use of the product in the treatment of postmenopausal osteoporosis. Actonel was promoted by the Alliance for Better Bone Health which was comprised of Procter & Gamble and Aventis Pharma. Merck Sharp & Dohme supplied Fosamax (alendronate).

Merck Sharp & Dohme stated that the detail aid made repeated references to 'non-vertebral fracture risk reduction', which included 'osteoporotic fractures of the hip, wrist, humerus, pelvis, clavicle and leg'. The population was 'postmenopausal women with low BMD [bone mineral density], with or without pre-existing fracture'. However, Actonel was licensed only for 'Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures'. Established osteoporosis was defined by the World Health Organisation (WHO) as a BMD below the WHO defined diagnostic threshold with a previous fracture. The claims made suggested a reduction in hip fractures in a patient group including those *without* a previous fracture. Actonel was only licensed for reducing the risk of hip fracture in patients with a previous fracture ('established osteoporosis').

The Panel noted that data presented on pages 3 and 5 of the detail aid showed a reduction in the risk of non-vertebral fracture in postmenopausal women with low BMD with or without a pre-existing fracture. This was therefore a mixed population ie patients with osteoporosis (those without a pre-existing fracture) and patients with established osteoporosis (those with a pre-existing fracture). Actonel was licensed to reduce the risk of vertebral fracture in the former group and to reduce the risk of hip fracture in the latter. The non-vertebral fracture data included hip fracture as well as fractures of the wrist, humerus, pelvis, clavicle and leg. The position was thus confusing as the non-vertebral fracture data included data relating to a reduction in the risk of hip fracture for which Actonel was licensed in patients with established osteoporosis but the patient population included some patients who did not have established osteoporosis. Pages 3 and 5 were headed 'In postmenopausal osteoporosis'; in the Panel's view without the qualification of 'established' this heading would be taken to mean patients without an existing fracture. In such a patient group Actonel was licensed to reduce the risk of vertebral fracture; reduction in the risk of non-vertebral fracture might also be a consequence of such therapy. There was no reason to assume that such sites would not include the hip. Reduction in the hip fracture risk was not promoted *per se* for such patients. Hip fracture was part of a composite of non-vertebral fracture. In that regard the Panel ruled no breach of the Code.

The Panel noted, however, that on page 3 the non-vertebral fracture data had been given equal prominence to the vertebral fracture data and that page 5 featured only non-vertebral fracture data. The Panel considered that it had not been made sufficiently clear that reduction in the risk of vertebral fractures was the primary reason to use Actonel in postmenopausal osteoporosis. Pages 3 and 5 of the detail aid were thus inconsistent with the summary of product characteristics (SPC) on this point and a breach of the Code was ruled.

Merck Sharp & Dohme Limited complained about a 12 page detail aid (ref ACT3191102) for Actonel (risedronate) which discussed the use of the product in the treatment of postmenopausal osteoporosis. Actonel was promoted by the Alliance for Better Bone Health which was comprised of Procter & Gamble Pharmaceuticals UK, Limited and Aventis Pharma Ltd and the matter was taken up with both companies. Merck Sharp & Dohme supplied Fosamax (alendronate).

COMPLAINT

Merck Sharp & Dohme stated that within the detail aid there were repeated references to 'non-vertebral facture risk reduction'. The non-vertebral fractures referred to included 'osteoporotic fractures of the hip, wrist, humerus, pelvis, clavicle and leg'. The population was 'postmenopausal women with low BMD [bone mineral density], with or without pre-existing fracture'. However, Actonel was licensed only for 'Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures'. There was no reference to fractures other than vertebral or hip fractures in the indication section or any other section of the Actonel summary of product characteristics (SPC). Merck Sharp & Dohme alleged that encouraging use of Actonel for non-vertebral fractures risk reduction was therefore a breach of Clause 3 of the Code.

Established osteoporosis was defined by the World Health Organisation (WHO) as a BMD below the WHO defined diagnostic threshold *with* a previous fracture. The claims made suggested a reduction in hip fractures in a patient group including those *without* a previous fracture. Actonel was only licensed for reducing the risk of hip fracture in patients with a previous fracture ('established osteoporosis'). Implying reduction in risk of hip fracture in those without a previous fracture was, Merck Sharp & Dohme alleged, in breach of Clause 3.

RESPONSE

Procter & Gamble and Aventis submitted a joint response from the Alliance for Better Bone Health. The Alliance did not accept that the claims it made were in breach of the Code. Actonel 35mg was indicated for 'Treatment of postmenopausal osteoporosis, to reduce the risk of vertebral fractures. Treatment of established postmenopausal osteoporosis, to reduce the risk of hip fractures'. The data were covered by the authorized indication, and were not inconsistent with the SPC.

The Alliance explained that the European Committee for Proprietary Medicinal Products (CPMP) provided guidance on the licensing of pharmaceutical products. The Note for Guidance (NfG) stated that to obtain the indication 'treatment of osteoporosis', 'The applicant will be requested to study the effect of the investigated drug on both spinal and femoral (not all non-vertebral) fractures… In the 'indication' part of the SPC, it will be clearly specified if anti-fracture efficacy has been shown at the spine and/or at the hip. Failure to demonstrate anti-fracture efficacy at the second site will also appear in this section of the SPC'. The NfG therefore included only vertebral and hip fractures as specific measures in the indication section of the SPC. This certainly did not imply that vertebral and hip fractures were the only clinical consequences of osteoporosis that were relevant to the physician or to the patient.

Prior to the adoption of the CPMP's NfG (January 2001) both Fosamax 10mg and Actonel 5mg had data in Section 5.1 of their respective SPCs to support fracture efficacy at a composite endpoint of non-vertebral sites. Since the adoption of the NfG, Actonel 5mg had been re-assessed through the mutual recognition procedure to include the hip fracture indication. As part of this process, reference to non-vertebral fracture was removed from Section 5.1, in line with the CPMP guidance. Actonel 35mg and Fosamax 70mg were both approved via the mutual recognition procedure after adoption of the CPMP guidance, and neither SPC included any non-vertebral fracture statement. The database supporting the efficacy of Actonel against non-vertebral fractures remained unchanged. Thus these changes to the SPC were based on an interpretation of the NfG which excluded anything other than vertebral and hip fractures in the indication section of the SPC and did not explicitly cover inclusion of non-vertebral fracture information in other sections of the SPC.

The Alliance stated that Actonel had demonstrated the required (by guideline) anti-fracture efficacy to obtain the indication 'treatment of osteoporosis'. Vertebral and hip fracture reduction effects were the only specific measures that were considered as an indication for any osteoporosis therapy, when supported by the appropriate data. However, as the Alliance had data to demonstrate Actonel's effect at reducing non-vertebral fractures in the treatment of osteoporosis, this claim was not inconsistent with the approved indication. Furthermore, non-vertebral fractures were undoubtedly important in the management of osteoporosis, and represented a significant burden to the UK health service. Within the population of England and Wales, a total of more than 110,000 cases of non-vertebral fracture were reported, compared to just 6,195 vertebral fractures and 19,179 hip fractures (van Staa, 2001). As osteoporosis was a systemic condition, it was medically relevant to know a product's effect on fractures at osteoporotic sites other than just the vertebrae and hip. In all of the Actonel clinical trials, non-vertebral fractures were defined as a composite endpoint of osteoporotic fracture sites: the wrist, humerus, hip, pelvis, leg, and clavicle. Non-vertebral fracture claims were not worded or illustrated in a way that could imply efficacy at any of these fracture

sites individually. Importantly, Actonel had been proven to reduce the risk of non-vertebral fractures in a number of randomised, controlled trials (Harris *et al*, 1999; McClung *et al*, 2001; Reginster *et al*, 2000). In addition, the specific data included in the detail aid (in patients with and without prior vertebral fracture) had recently been accepted for publication in a peer-reviewed journal (Harrington *et al*, 2003 in press). It was undisputed that Actonel had proven efficacy in reducing the risk of non-vertebral fractures.

In brief, non-vertebral fractures were a consequence of the primary condition, osteoporosis, and Actonel had been demonstrated to its full capacity under the guidance to treat osteoporosis.

Case AUTH/819/1/99 provided a relevant perspective. This case concerned the promotion of Zocor (simvastatin) which was indicated for patients with coronary heart disease and raised cholesterol levels to reduce the risk of mortality, coronary death and myocardial infarction (and other associated risks). Claims were made on the effect of Zocor on angina. These claims were challenged on the basis of angina being outside the licensed indications for Zocor. However, in considering the case, the Panel had noted that angina was a clinical manifestation of the underlying disease process for which the medicine was indicated. No breach of the Code had been ruled. The Alliance submitted that this case provided a useful parallel, in that non-vertebral fractures were a clinical manifestation of the underlying disease process, osteoporosis, which Actonel was indicated to treat.

In summary, Actonel had demonstrated the required anti-fracture efficacy to obtain the indication 'treatment of osteoporosis' under the mutual recognition procedure. The Alliance had data to demonstrate Actonel's efficacy in reducing non-vertebral fractures in the treatment of postmenopausal osteoporosis, and therefore non-vertebral fracture claims were covered by the approved indication, and were not inconsistent with the SPC. The Alliance therefore submitted that its material complied with the Code.

PANEL RULING

The Panel noted that a banner, which read 'In postmenopausal osteoporosis', ran across the top of pages 1 to 5 of the detail aid. Page 1, the front cover, featured the photograph of the body of a woman sitting with her back to the camera and her head bowed. Across the lumbar spine region of her back her body was superimposed with the word 'AIRBAG'. Next to the woman's photograph, and presumably referring to the airbag was: 'If only protection from fractures was this immediate …'. Page 2 headed 'Introducing The Actonel Advantage' also featured the photograph of the woman but this time her head was raised and she was looking to the right and across her lumbar spine was superimposed the Actonel product logo. Next to the woman's photograph, and in a line with the superimposed product logo, was 'Advanced protection from fractures'.

Page 3 of the detail aid headed 'Significant protection within months – not years' featured two graphs; the first showed the clinical vertebral fracture risk reduction of Actonel vs control over one year in postmenopausal women with at least 1 pre-existing vertebral fracture. The second graph showed the non-vertebral fracture risk reduction of Actonel vs control over one year in postmenopausal women with low BMD with or without pre-existing vertebral fracture. With regard to both graphs the difference between Actonel and control was significant at 6 months in favour of Actonel. At 12 months there was a 69% risk reduction in clinical vertebral fracture ($p<0.01$) and a 74% risk reduction for non-vertebral fractures ($p<0.05$) for patients on Actonel vs control.

Pages 4 and 5 were both headed 'Actonel gives significant protection within months'. Page 4 detailed the clinical vertebral fracture risk reduction data and repeated the first graph shown on page 3 as well as showing comparable data for alendronate. Page 5 gave details of non-vertebral fracture risk reduction and showed an extension of the second graph from page 3 again with comparable data for alendronate. The non-vertebral fractures referred to were osteoporotic fractures of the hip, wrist, humerus, pelvis, clavicle and leg. For alendronate the non-vertebral fractures were osteoporotic fractures which occurred at any site excluding the skull or face.

Actonel was licensed for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral fractures and for the treatment of established postmenopausal osteoporosis to reduce the risk of hip fractures. The CPMP NfG on postmenopausal osteoporosis in women stated that such a licence was dependent upon studying the effects of a medicine on both spinal and femoral fractures and being able to show anti-fracture efficacy at at least one site and no deleterious effect at the other. The 'indications' section of the SPC would clearly specify the site(s) at which anti-fracture efficacy had been shown. Failure to demonstrate anti-fracture efficacy at the second site would also appear at that section of the SPC.

The Panel noted that osteoporosis was a systemic disorder which resulted in increased bone fragility and susceptibility to fracture. Loss of bone mass in osteoporotic patients generally involved the entire skeleton. In the Panel's view, although a marketing authorization was granted upon a medicine's anti-fracture efficacy at the spine and/or the hip (and no deleterious effect on either) it was reasonable to assume that the product might, at the same time, also demonstrate some anti-fracture efficacy at other sites. Nonetheless the Code required a medicine to be promoted in accordance with the terms of its marketing authorization.

The Panel noted that data presented on pages 3 and 5 of the detail aid showed a reduction in the risk of non-vertebral fracture in postmenopausal women with low BMD with or without a pre-existing fracture. This was therefore a mixed population ie patients with osteoporosis (those without a pre-existing fracture) and patients with established osteoporosis (those with a pre-existing fracture). Actonel was licensed to reduce the risk of vertebral fracture in the former group and to reduce the risk of hip fracture in the latter. The non-vertebral fracture data included hip fracture as well as fractures of the wrist, humerus,

pelvis, clavicle and leg. The position was thus confusing as the non-vertebral fracture data included data relating to a reduction in the risk of hip fracture for which Actonel was licensed in patients with established osteoporosis but the patient population included some patients who did not have established osteoporosis. Pages 3 and 5 were headed 'In postmenopausal osteoporosis'; in the Panel's view without the qualification of 'established' this heading would be taken to mean patients without an existing fracture. In such a patient group Actonel was licensed to reduce the risk of vertebral fracture; reduction in the risk of non-vertebral fracture might also be a consequence of such therapy. There was no reason to assume that such sites would not include the hip. Reduction in the hip fracture risk was not promoted *per se* for such patients. Hip fracture was part of a composite of non-vertebral fracture. In that regard the Panel ruled no breach of Clause 3.2 of the Code.

The Panel noted however, that on page 3 the non-vertebral fracture data had been given equal prominence to the vertebral fracture data and that page 5 featured only non-vertebral fracture data. The Panel considered that it had not been made sufficiently clear that reduction in the risk of vertebral fractures was the primary reason to use Actonel in postmenopausal osteoporosis. Pages 3 and 5 of the detail aid were thus inconsistent with the SPC on this point and a breach of Clause 3.2 was ruled.

Complaint received **21 May 2003**

Case completed **22 July 2003**

CASE AUTH/1473/6/03 ***NO BREACH OF THE CODE***

MEDIA/DIRECTOR v NOVARTIS

Stepwise campaign

An article entitled 'Regulator spells out rules on disease awareness campaigns' in the BMJ referred to the Disease Awareness Campaigns (DAC) Guidelines issued by the Medicines and Healthcare products Regulatory Agency (MHRA) and criticised the Stepwise campaign run by Novartis. In accordance with established procedures regarding public criticism of the industry, the matter was taken up by the Director as a complaint under the Code.

The article referred to an advertisement which stated: 'The infection can spread to other nails, other parts of your body and to other people and it won't go away without effective treatment from your GP'. The author queried what sort of effective treatment would be available? Among the few medicines recommended in guidelines from The British Society for Medical Mycology was the prescription only medicine terbinafine (Lamisil), manufactured by Novartis.

The author noted that the MHRA guidelines stated that while a disease awareness campaign might refer to the availability of treatment options, 'this should not be of such a nature that an individual would be encouraged to approach a prescriber to request a particular medicinal option'. But the final page of a website cited by the Novartis campaign stated that '… although it may be possible to buy treatments for fungal nail infection ... the most effective ones are only available from your doctor'. The author questioned whether there was a danger that someone who had never previously heard of fungal nail infection but who now realised they might have it might approach their GP to ask for the 'most effective treatment' and that faced with such request the GP might prescribe terbinafine? Was this not direct to consumer advertising by the back door?

The author noted that the MHRA guidelines stated 'DACs for diseases or conditions where there is only one, one leading or few medicinal treatments potentially draw attention to one medicinal product, albeit indirectly, regardless of whether it is referred to or not. DACs in these circumstances require particular care'. The guidelines did not make clear what 'particular care' meant, although the Department of Health (DoH) stated that this meant that campaigns should not promote any particular prescription only medicine. The DoH stated that as long as the Novartis campaign did not steer consumers toward a particular product, it would not be in breach of the guidelines.

The Panel considered that it could not rule on whether the material breached the MHRA's DAC Guidelines. The 2001 edition of the Code predated the MHRA DAC Guidelines; they were referred to in the 2003 edition of the Code which came into operation on 1 July 2003.

It appeared to the Panel that the author considered that Novartis, by encouraging patients to seek help from their doctor because '[fungal nail infections] won't go away without effective treatment from your GP' and stating that 'the most effective [treatments] are only available from your doctor', was effectively advertising its prescription only medicine, Lamisil, directly to the general public. The Panel noted, however, that Lamisil was not the only medicine for fungal nail infection which was only available from a doctor. Further, of the prescription only medicines which were available some were to be taken orally and others were to be applied topically.

The Stepwise patient booklet stated 'If you have tried over-the-counter products for fungal nail infection that haven't worked, you should talk to your GP who can prescribe effective treatments that do' and further that once the doctor has decided to treat the fungal nail infection then either an oral treatment might be prescribed or a topical therapy.

In a section of the booklet headed 'What treatments are available for fungal nail infection?' patients were told that there were a number available; a limited selection was available from the local pharmacy but the most effective ones were only available from a doctor. It was stated that the different types of treatment generally prescribed by doctors were oral treatments or lacquers/solutions. Information regarding the length of treatment was given. Patients were advised that creams might also be used to treat certain types of fungal nail infection. The stepwise website contained similar statements and invited readers to apply for a copy of the booklet.

The Panel noted that although data showed that Lamisil was more than three times more likely to be prescribed than its nearest competitor, the decision to prescribe anything at all still lay with the GP.

The Stepwise material encouraged patients to seek medical help for their fungal nail infection but did not encourage them to ask for any particular form of treatment. The Panel did not consider that the Stepwise materials amounted to an advertisement to the general public for Lamisil. No breach of the Code was ruled. The Panel also did not consider that the materials would encourage patients to ask their doctors to prescribe Lamisil and so ruled no breach of the Code.

An article entitled 'Regulator spells out rules on disease awareness campaigns' in the BMJ on 31 May 2003 referred to the Disease Awareness Campaigns (DAC) Guidelines issued by the Medicines and Healthcare products Regulatory Agency (MHRA) and was critical of the Stepwise campaign run by Novartis Pharmaceuticals UK Ltd to raise awareness of fungal nail infections.

There had been a number of previous cases about the Stepwise campaign, most recently Case AUTH/1350/8/02. Paragraph 5.1 of the Constitution and Procedure stated that if a complaint concerned a matter closely similar to one which has been the subject of a previous adjudication, it might be allowed to proceed at the discretion of the Director of the Authority if new evidence was adduced by the complainant or if the passage of time or a change in circumstances raised doubts as to whether the same decision would be made in respect of the current complaint. Further, the Director should normally allow a complaint to proceed if it covered matters similar to those in a decision of the Code of Practice Panel which was not the subject of an appeal to the Code of Practice Appeal Board.

Since Case AUTH/1350/8/02 was completed the MHRA had issued the DAC Guidelines referred to by the author of the article. Also the author of the BMJ article raised the issue that given the high market share of Lamisil anyone going to their doctor and asking for the 'most effective treatment' was likely to be given a prescription for the product. The materials were different to those considered previously. Taking all the circumstances into account, and in accordance with established procedures regarding public criticism of the industry, the matter was taken up by the Director as a complaint under the Code.

COMPLAINT

The article referred to an advertisement which stated: 'The infection can spread to other nails, other parts of your body and to other people and it won't go away without effective treatment from your GP'. The author queried what sort of effective treatment would be available? Among the few medicines recommended in guidelines from The British Society for Medical Mycology was the prescription only medicine terbinafine (Lamisil), manufactured by Novartis.

The author noted that the MHRA guidelines stated that whilst a disease awareness campaign might refer to the availability of treatment options, 'this should not be of such a nature that an individual would be encouraged to approach a prescriber to request a particular medicinal option'. The final page of a website cited by the Novartis campaign stated 'Please note, although it may be possible to buy treatments for fungal nail infection over-the-counter [OTC] at your pharmacy, the most effective ones are only available from your doctor' (www.stepwise-uk.com). The author questioned whether there was a danger that someone who had never previously heard of fungal nail infection but who now realised they might have it might approach their GP to ask for the 'most effective treatment'? And was there then not the chance that a GP faced with that request might prescribe terbinafine? Was this not direct to consumer advertising by the back door?

The author noted that Novartis denied that the Stepwise campaign was direct to consumer advertising stating that there were 11 products available for fungal nail infections, including OTC preparations. Novartis also explained that this year its share of the market had declined from 65% to 55%, suggesting that the campaign was encouraging people to seek OTC products.

The author noted that the MHRA guidelines stated 'DACs for diseases or conditions where there is only one, one leading or few medicinal treatments potentially draw attention to one medicinal product, albeit indirectly, regardless of whether it is referred to or not. DACs in these circumstances require particular care'. The guidelines did not make clear what exactly 'particular care' meant, although the Department of Health (DoH) stated that this meant that campaigns should not promote any particular prescription only medicine. The DoH stated that as long as the Novartis campaign did not steer consumers toward a particular product, it would not be in breach of the guidelines.

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

RESPONSE

Novartis stated that the article in question which formed part of an edition of the BMJ reviewing all aspects of the relationships between doctors and the pharmaceutical industry, claimed to raise doubts over the suitability of disease awareness campaigns in general using the Stepwise campaign as an example.

The author interpreted the statements contained in the materials and the guidelines of the British Society for Medical Mycology to imply that the Stepwise programme was unacceptable and promoted Lamisil. As the company had demonstrated in previous responses to the Authority, the Stepwise materials contained no reference to any specific medicinal therapies whether purchased or prescribed.

The author implied that the guidelines of the British Society for Medical Mycology had singled out Lamisil as among the few medicines recommended. However, the guidelines referred to the majority of currently available topical and systemic treatments for fungal nail infection in a balanced fashion. The guidelines made no reference to relative efficacy as implied by the author.

The effective treatments available from the GP, as referred to in the Stepwise material, included a number of prescription medicines including amorolfine, tioconazole, griseofulvin, intraconazole and terbinafine. Clearly a GP could also prescribe an OTC or pharmacy (P) medicine which increased the options available to a dozen or so products. This matter had been raised as part of previous complaints and Novartis believed that this had been resolved to the satisfaction of the Panel and the Appeal Board (Cases AUTH/313/6/95, AUTH/516/3/97 and AUTH/1350/8/02).

As previously noted people who responded to the Stepwise advertisement were likely to have already identified that they had some concerns about nail infection and were seeking advice and guidance. They might have noted for themselves a progression of their athlete's foot or a gradual deterioration of their nails.

Research carried out on patients who had responded to the Stepwise advertisement showed that on average, they had had their infection for over 3 years in three or four nails. It was clear that by the time the patient's nails had reached this level of deterioration, spontaneous resolution was not a possibility and successful self medication had become highly unlikely. Such failure might lead the patient to consider their condition untreatable. These were exactly the patients for whom the Stepwise materials were designed to avoid such an outcome and ensure that they received appropriate treatment and advice and wherever possible were removed from the infectious pool.

Novartis was surprised by the author's suggestion therefore that a patient visiting their GP with such a concern about their fungal infection would request anything other than an effective treatment. Given that the patient had been given no information on any product whether prescription, OTC, topical or systemic by the Stepwise materials the decision regarding the medicine selected as most effective for that patient remained entirely with the prescriber.

With regard to market share of the products prescribed for the treatment of fungal nail infection Lamisil was not the only medicine considered to be an 'effective treatment' by general practitioners. Indeed, as quoted in the BMJ article, there had been a decline in the product's market share over the last 4 years with a steady increase in the main competitors' shares over the same period. This demonstrated that whilst Stepwise might raise the overall number of patients seeking appropriate treatment for nail infection, it was not leading to a disproportionate market share increase for any particular product.

In conclusion, Novartis was confident that the Stepwise materials continued to conform to the Code. In addition, the materials were in accord with the requirements of the new MHRA guidelines. As the author noted in the final paragraph of the article 'A DoH spokesman [asked to comment on the acceptability of the Stepwise material] said that as long as the Novartis campaign did not steer consumers towards a particular product, it would not be in breach of the guidelines'.

PANEL RULING

The Panel considered that patient education programmes about a disease area were a legitimate activity for a pharmaceutical company to undertake. Such activity had to comply with the Code. Although disease awareness campaigns might facilitate the market development of the sponsoring company's products this was not necessarily in breach of the Code. Each case would need to be judged on its merits. The Panel could only rule on the requirements of the Code. It could not rule on whether the material breached the MHRA's DAC Guidelines. The 2001 edition of the Code predated the MHRA DAC Guidelines; they were referred to in the 2003 edition of the Code which came into operation on 1 July 2003.

The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines and certain other medicines to the general public. Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

It appeared to the Panel that the author considered that Novartis, by encouraging patients to seek help from their doctor because '[fungal nail infections] won't go away without effective treatment from your GP' and stating that 'the most effective [treatments for fungal nail infections] are only available from your doctor', was effectively advertising its prescription only medicine, Lamisil, directly to the general public. The Panel noted, however, that Lamisil was not the only medicine for fungal nail infection which was only available from a doctor. Further, of the prescription only medicines which were available some were to be taken orally and others were to be applied topically.

The patient booklet, issued as part of the Stepwise campaign, gave advice on what patients could do about their fungal nail infection. Patients were told 'If you have tried over-the-counter products for fungal nail infection that haven't worked, you should talk to your GP who can prescribe effective treatments that

do' and further that once the doctor has decided to treat the fungal nail infection then either an oral treatment might be prescribed or a topical therapy. In a section of the booklet headed 'What treatments are available for fungal nail infection?' patients were told that there were a number available; a limited selection was available from the local pharmacy but the most effective ones were only available from a doctor. It was stated that the different types of treatment generally prescribed by doctors were oral treatments or lacquers/solutions. Information regarding the length of treatment was given. Patients were advised that creams might also be used to treat certain types of fungal nail infection. The website (www.stepwise-uk.com) contained similar statements and invited readers to apply for a copy of the booklet.

The Panel noted from the market share data (moving annual totals) provided by Novartis that the number of patients being treated with anti-fungals had increased by over 45% in three years since April 2000. The market had thus expanded although Lamisil's share of that market had decreased from 55.6% to 50.8%. The nearest competitor currently had a 15.4% market share. The Panel noted that although Lamisil was more than three times more likely to be prescribed than its nearest competitor the decision to prescribe anything at all still lay with the GP.

The Stepwise material encouraged patients to seek medical help for their fungal nail infection but did not encourage them to ask for any particular form of treatment. The Panel did not consider that the Stepwise materials amounted to an advertisement to the general public for Lamisil. No breach of Clause 20.1 was ruled. The Panel also did not consider that the materials would encourage patients to ask their doctors to prescribe Lamisil and so ruled no breach of Clause 20.2 of the Code.

Proceedings commenced 5 June 2003

Case completed 4 August 2003

CASE AUTH/1474/6/03

ROCHE v SCHERING-PLOUGH

Promotion of ViraferonPeg

Roche complained about the promotion of ViraferonPeg (peginterferon alfa-2b) by Schering-Plough. The material at issue, a booklet entitled 'Does body weight impact HCV [hepatitis C virus] treatment efficacy? A Critical Review From Landmark Trials February 2003', was alleged to be disguised promotion as it contained no reference as to where or by whom it was produced. It looked like an independent paper but was being used promotionally by Schering-Plough; there was no prescribing information. Roche also complained about telephone calls made subsequent to the booklet's distribution. Roche supplied Pegasys (peginterferon alfa-2a). ViraferonPeg was given on a mcg/kg bodyweight basis whereas Pegasys was given as a fixed dose regardless of weight.

The Panel noted that the Schering-Plough gastro salesforce were each provided with 60 copies of the booklet which was a discussion of the data upon weight as a predictor of response in achieving a sustained viral response (SVR) when treating with interferons. The booklet could be used by representatives to discuss issues surrounding the session and it could be left with customers at their request.

The Panel considered the booklet was clearly being used for a promotional purpose; it gave the impression that it was an independent publication and that was not so. There was no mention of Schering-Plough or explanation of the company's role in the booklet's creation and sponsorship. The booklet did not have the appearance of a promotional item. The booklet favourably compared Schering Plough's product, peginterferon alfa-2b, with the Roche product. The Panel considered that the booklet was disguised promotion for ViraferonPeg; a breach of the Code was ruled. The booklet did not contain prescribing information for ViraferonPeg and a breach of the Code was ruled.

Roche noted that the claim '… McHutchison and Poynard introduced the notion that factors such as genotype, age, and particularly weight, affected SVR outcomes' appeared beneath the heading 'McHutchison and Poynard reported that weight is a predictive factor for response with fixed dose [interferon] alfa-2b monotherapy'. Roche stated that Poynard *et al* did not mention weight as a predictor of achieving a SVR whilst McHutchison *et al* stated that SVR was unrelated to age, sex and bodyweight. Evidence to date demonstrated that the most important factor in obtaining an SVR was the hepatitis C genotype. Other predictors of response shown to be more important than weight included baseline viral load, presence/absence of fibrosis and age. Roche alleged that the phrase 'particularly weight' was therefore deliberately erroneous and misled the reader into believing bodyweight was the most important factor in obtaining an SVR and did not reflect the totality of current scientific opinion.

The Panel considered that the claim at issue was inaccurate. McHutchison *et al* stated that SVR was unrelated to, *inter alia*, bodyweight and Poynard *et al* did not discuss weight as a predictive factor. The emphasis created by the use of the word 'particularly' was compounded by the heading 'McHutchison and Poynard reported that weight is a predictive factor for response with fixed dose [interferon] alfa-2b monotherapy'. The claim was inaccurate, misleading and could not be substantiated; breaches of the Code were ruled.

Roche stated that the continued focus of the booklet over-emphasised bodyweight as the main predictor of outcome in hepatitis C therapy and implied superiority of any interferon that was dosed by bodyweight (ie ViraferonPeg) over one that was a fixed dose (ie Pegasys). This was done, for example, by emboldened headlines such as 'Zeuzem and Heathcote reported that weight is a predictive factor for response with fixed dose PEG-IFN alfa-2a monotherapy'. There was no mention of bodyweight as a factor associated with outcome in Heathcote *et al* whilst in Zeuzem *et al* bodyweight was found not to be a factor but body surface area was. This was misleading and the references inaccurate.

Roche alleged that claims such as: 'Individualized weight adjusted PEG-IFN alfa-2b plus ribavirin therapy maximizes the chance for SVR in the broadest HCV population' and 'The results reported in all the landmark trials suggest that weight adjusted therapy is necessary to maximise the chance for an SVR in the broadest population of patients with HCV' disparaged and reduced confidence in Pegasys especially when put into context with the statements in the booklet which exaggerated the efficacy of ViraferonPeg.

Looking at subgroups of those patients with genotype 2/3, those patients with high viral loads and those with fibrosis/cirrhosis, there was no evidence to claim superiority in the 'broadest population of HCV patients'. Manns *et al* stated that the 'primary benefit of peginterferon alfa-2b plus ribavirin for this group (genotype 2/3) may be convenience, ease of administration of a once-weekly injection compared with alternate-day injections and the potential for better compliance' and again conflicted with the message of superiority in the 'broadest population of HCV patients' and 'maximises the chance for an SVR'. Therefore this was an exaggerated claim.

The entire document over-emphasised the importance of weight in achieving an SVR and suggested that an interferon that was dosed by weight would not overcome this and so exaggerated the efficacy of ViraferonPeg and disparaged the clinical data on Pegasys. The evidence suggested that many factors were important in achieving an SVR in hepatitis C. Whilst weight was a factor in some studies, viral load, age and particularly genotype were more important.

The Panel considered that the emboldened headline claim 'Zeuzem and Heathcote reported that weight is a predictive factor for response with fixed dose PEG-IFN alpha-2a monotherapy' was incorrect. Whilst subsequent text on the facing page and in a less prominent typeface presented some data from Zeuzem *et al* in relation to, *inter alia*, body surface area and described body surface area as a surrogate for weight it did not negate the overall impression created by the headline. The Panel further noted that Schering-Plough accepted that the reference to Heathcote was incorrect. The Panel considered the claim misleading and not capable of substantation as alleged; breaches of the Code were ruled.

The Panel considered that the individual and cumulative effect of the claims cited by Roche was to cast doubt upon the efficacy of the licensed dose for Pegasys. This was compounded further by the broad claims such as 'Individualized weight adjusted PEG-IFN alfa-2b plus ribavirin therapy maximizes the chance for SVR in the broadest HCV population' and 'The results reported in all the landmark trials suggested that weight adjusted therapy is necessary to maximize the chance for an SVR in the broadest population of patients with HCV'. The Panel considered that the booklet was designed to disparage the licensed dosing regimen of Pegasys as alleged; a breach of the Code was ruled.

The Panel considered that the claim 'Individualised weight adjusted PEG-IFN alfa-2b plus ribavirin therapy maximizes the chance for SVR in the broadest HCV population' was not a fair reflection of the data in Mann *et al*. The benefit achieved with the most effective regimen of 1.5mcg/kg per week was achieved mainly in patients with types 2 and 3 genotype. Weight was not a significant independent predictor of response when control for ribavirin dose was taken into account. The claim exaggerated the data; a breach of the Code was ruled.

Roche understood that provision of the booklet was followed up by a telephone call which would discuss the booklet and was described as 'Independent Research'. If this were to happen this would be disguised promotion.

The Panel noted Schering-Plough's submission that the follow-up telephone calls were undertaken in conjunction with an independent market research agency and that it was not privy to whom the market research agency contacted. The Panel noted that the questionnaire was very detailed and covered product usage, the recollection of discussions on ViraferonPeg and the future prescribing intentions. The Panel noted Schering-Plough's submission that the questions were intended to help the company understand the customer's perception of any message or product. The Panel considered that the questions were designed to assist the company as stated rather than to promote ViraferonPeg as alleged. No breach of the Code was ruled.

Roche Products Ltd complained about the promotion of ViraferonPeg (peginterferon alfa-2b) by Schering-Plough Ltd.

The material at issue was a booklet entitled 'Does body weight impact HCV treatment efficacy? A Critical Review From Landmark Trials February 2003' and telephone calls made subsequent to its distribution.

Roche also had a product, Pegasys (peginterferon alfa-2a). Both products were licensed for the treatment of chronic hepatitis C.

GENERAL COMMENTS FROM ROCHE

Roche stated that both Pegasys and ViraferonPeg were licensed for the treatment of chronic hepatitis C and were given as once weekly injections, usually in combination with ribavirin. Both were pegylated interferons but differed in the size and structure of their molecules. This meant they had different pharmacological properties, such that Pegasys was

dosed at 180mcg for all patients, irrespective of weight, whereas ViraferonPeg was given on a mcg/kg bodyweight basis.

The licensed dose of Pegasys was 180mcg whether given as monotherapy or in combination with ribavirin. The licensed dose of ViraferonPeg was 1mcg/kg as monotherapy and 1.5mcg/kg in combination with ribavirin.

The aim of treating hepatitis C was to eradicate the virus and so prevent progression of liver disease. This was measured as a sustained viral response (SVR). A number of baseline factors might affect the outcome of therapy, but the genotype of the hepatitis C virus had been shown to be the predominant factor. Other important factors included pre-treatment viral load, age, and baseline hepatic fibrosis. Weight had also been found to be a predictor of outcome but was not as important as the above variables.

GENERAL COMMENTS FROM SCHERING-PLOUGH

Schering-Plough denied the allegation that its activities could lead to the use of unlicensed doses of Pegasys which could compromise patient outcomes. It did not, and would not, promote a dosage for a product outside its licence; especially another company's product.

Clearly Pegasys should not be dosed outside its licence. Members of the sales force had all been trained on the Code and were aware of what they were permitted to discuss. In a spirit of co-operation, acting on an earlier unsubstantiated allegation by Roche, Schering-Plough had sent out instructions reminding the sales force of its responsibilities. Schering-Plough stated that its representatives were briefed to detail the company's products ViraferonPeg and Rebetol (ribavirin); they were not trained, or encouraged to comment on the posology of Pegasys.

Roche referred to Schering-Plough's frequent references to the FDA both in its written and verbal communications with health professionals attempting to legitimise the campaign which over-emphasised the importance of bodyweight in hepatitis C. In the absence of evidence that there had been any verbal communication regarding the FDA Schering-Plough could only focus on the document in hand.

The wealth of data, from all the pivotal trials, demonstrated the significance of bodyweight as a prognostic factor when antiviral therapy was flat dosed. If making this point was a 'campaign', then it did not require third party support to 'legitimise' it. The data was robust enough. The FDA analysis was in the public domain, and represented an elegant, third party analysis of data, which the company had otherwise not released. No endorsement of a particular stance was made. Schering-Plough did not, for example state 'FDA approved'. It simply used this site as a convenient source of currently unpublished data.

A Booklet entitled 'Does body weight impact HCV treatment efficacy? A Critical Review From Landmark Trials February 2003'

The booklet discussed weight as a predictive factor for SVR in the treatment of hepatitis C.

Roche stated that the booklet was originally given out at a global investigators event held in London in February 2003 but was now given to customers unsolicited and used as a promotional aid. It had been used by representatives on exhibition stands such as at the Scottish Hepatitis meeting in Stirling on 28 May 2003 and examples of its distribution to health professionals throughout the UK were provided.

GENERAL COMMENTS FROM SCHERING-PLOUGH ON THE BOOKLET AND BODYWEIGHT

Schering-Plough stated that clearly the discussion of weight as a prognostic factor for cure in hepatitis C was germane and noted that Roche had made it clear that it supported the position that weight impacted on cure in chronic hepatitis C. The key issue in the complaint appeared to be that the entire document over-emphasised the importance of weight in achieving an SVR and suggested that an interferon that was dosed by weight would overcome this and so exaggerated the efficacy of ViraferonPeg and disparaged the clinical data on Pegasys.

Schering-Plough noted that patient weight was one of the top three or four factors in achieving an SVR. Its relative role was put in context in the first two figures of the booklet. But in a booklet entitled 'Does bodyweight impact HCV treatment efficacy?' it was hardly surprising that most of the booklet was devoted to this topic.

Schering-Plough stated that Roche had made a fundamental error. The data, as laid out in the booklet, was clear that all components of the antiviral therapy needed to be dosed by weight if a patient's weight was to be removed as a prognostic factor as demonstrated in the booklet and summarised below. Clearly when the older, less effective interferon monotherapy was considered then it was true to say that weight based dosing overcame patient weight as a prognostic factor and Schering-Plough demonstrated this in the booklet and below.

ViraferonPeg, licensed to be used as a weight-based therapy, with or without the combination of weight-based ribavirin, when given as licensed, had the same effect in heavy or light patients. As demonstrated in the booklet, and summarised below, this was the consensus of medical opinion, and represented the body of evidence. Similarly, when Schering-Plough summarised the data that demonstrated that when Pegasys was given appropriately (flat dosed) the evidence showed that irrespective of any other potential virtue this product might have, patient weight became an independent prognostic factor. This represented the actual data, and did not disparage it.

Schering-Plough stated that it made the case, supported by the data, that flat dosing of antivirals in patients with chronic hepatitis C meant that bodyweight was an independent prognostic factor for cure. On the other hand, weight-based dosing of antiviral therapy in this group of patients removed weight as an independent prognostic factor. This was borne out by analyses of all the pivotal registration trials in this area.

Schering-Plough summarised the evidence as follows:

Zeuzem *et al* (2000) studied 531 patients with chronic hepatitis C and showed that body surface area was an independent factor associated with a sustained viral response when Pegasys was given as a fixed dose. Body surface area could be taken as a surrogate for weight.

A meta-analysis performed by Lee *et al* (2002) looked at 814 patients treated with flat dosed pegylated interferon alfa-2a in 3 large trials and reported that body weight was a prognostic factor for an SVR.

Similar results were obtained from the registration trial of 1121 patients with hepatitis C by Fried *et al* (2002); flat dosing of pegylated interferon alfa-2a was given in combination with ribavirin. The results were consistent with the findings of the registration trials of flat dosed interferon alfa monotherapy. Using a multiple logistic-regression model the authors concluded (among other factors) that a bodyweight ≤ 75kg 'independently and significantly' increased the chance of a cure.

Similarly Roche agreed that the prospective study by Hadziyannis *et al* showed that there was a decrease in SVR with an increase in bodyweight.

In-house post-hoc analyses of the data from the pivotal registration trails with flat dosed interferon alfa-2b in chronic hepatitis C (McHutchison *et al* 1998 and Poynard *et al* 1998) in 806 patients showed SVR (cure) rates of 32% with patients weighing < 55kg, 19% in patients 55-75kg, 13% in patients 75-95kg and only 9% in patients > 95 kg respectively.

The weight of evidence from registration studies published in peer reviewed journals supported the contention that a patient's weight was a significant prognostic factor when interferons were flat dosed.

Schering-Plough disagreed that stating that the available evidence demonstrated that a patient's weight affected the SVR achievable with any flat based dosed interferon, including its own, disparaged Pegasys.

Having accepted that flat dosing with Pegasys, and other interferons led to a lower SVR in heavier patients, Roche leapt into the statement that this was the same when antiviral therapy was dosed according to bodyweight. This was not so. The large pivotal studies in which antiviral therapies in chronic hepatitis C were dosed according to the patient's weight all showed that weight could be removed as a prognostic factor.

In the pivotal study with 1219 patients looking at weight-based pegylated interferon alfa-2b (ViraferonPeg) therapy in patients with chronic hepatitis C, Lindsay *et al* (2001) performed a logistic regression analysis of independent predictive factors for cure. With weight-based dosing the weight of the patient did not influence the chance of cure.

Similarly the pivotal trial of combination therapy with pegylated interferon, Manns *et al* (2001) concluded that when both components of the antiviral therapy were given according to the patient's weight (in accordance with the UK summary of product characteristics (SPC)) patient's weight as a predictor of response 'was no longer significant'. (Perhaps Roche was being a little disingenuous when using the non-licensed doses of the combination – where one half of the pair was not weight-based dosed to suggest this study showed weight-based dosing did not remove a patient's weight as a prognostic factor.)

In conclusion the data were clear on this point: Antiviral therapy for chronic hepatitis C, be it ViraferonPeg monotherapy or ViraferonPeg and ribavirin in combination, when given according to its licence, ie according to the patient's weight removed patient weight as an independent prognostic factor; the intuitive conclusion was reached that heavier patients did as well as lighter patients. When Pegasys was flat dosed, in accordance with its licence, lighter patients responded better than heavier patients.

Even if any or all of the theories regarding the association of steatosis, interferon resistance, sanctuary sites, and increased alcohol consumption were found to be true, it would deflect from the fact that weight-based dosing of antivirals in this condition removed a patient's weight as a prognostic factor for cure.

1 Alleged disguised promotion and absence of prescribing information

COMPLAINT

Roche alleged that the booklet was disguised promotion, in breach of Clause 10.1, as it contained no reference as to where or by whom it was produced. It was designed to look like an independent paper but was being used promotionally and being given out by Schering-Plough representatives.

There was no prescribing information and a breach of Clause 4.1 was also alleged.

RESPONSE

Schering-Plough strongly defended the basic conclusion of the booklet, namely that weight-based dosed antiviral therapy, like ViraferonPeg, reduced the risk of heavier patients being denied a cure. The company accepted in hindsight, that the format of the booklet was in breach of the Code, particularly its lack of prescribing information. Schering-Plough was therefore withdrawing this piece.

PANEL RULING

Clause 10.1 of the Code required that promotional material and activities were not disguised. The supplementary information to Clause 10.1 referred to the need for companies to declare sponsorship on company sponsored material.

The Panel noted Roche's general submission about how the item was used. Schering-Plough did not comment on this but provided a copy of a memorandum to its gastro salesforce dated 15 April entitled 'Does body weight impact HCV treatment efficacy?' monograph briefing document' under cover of which each representative was provided with 60 copies of the booklet at issue. The memorandum explained that the booklet was developed from a high

level scientific discussion of the data upon weight as a predictor of response in achieving an SVR when treating with interferons at a recent London meeting attended by key opinion leaders. The booklet could be used by representatives to discuss issues surrounding the session or questions about data related to the role of weight as a prognostic factor in achieving SVR. The booklet could be left with customers at their request.

The Panel noted the content of the memorandum and the number of booklets provided to the sales force for distribution. The Panel considered the booklet was clearly being used for a promotional purpose. The booklet gave the impression that it was an independent publication; that was not so. There was no mention of Schering-Plough or explanation of the company's role in the booklet's creation and sponsorship. The booklet did not have the appearance of a promotional item. The subtitle of the booklet 'A Critical Review From Landmark Trials February 2003' compounded the initial impression given.

The booklet favourably compared Schering Plough's product, peginterferon alfa-2b with the Roche product. The Panel considered that the booklet was disguised promotion for ViraferonPeg; a breach of Clause 10.1 was ruled. The booklet did not contain prescribing information for ViraferonPeg and a breach of Clause 4.1 was ruled.

2 Statement 'In the landmark studies published in the late 90s, McHutchison and Poynard introduced the notion that factors such as genotype, age, and particularly weight, affected SVR outcomes'

This statement appeared on page 2 beneath the heading 'McHutchison and Poynard reported that weight is a predictive factor for response with fixed dose [interferon] alfa-2b monotherapy'.

COMPLAINT

Roche stated that Poynard *et al* did not mention weight as a predictor of achieving a SVR whilst McHutchison *et al* stated that SVR was unrelated to age, sex and bodyweight.

All the pivotal studies performed so far in the treatment of hepatitis C; McHutchison *et al*, Poynard *et al*, Manns *et al*, Lindsay *et al*, Heathcote *et al* (2000), Zeuzem *et al* , Fried *et al* and Hadziyannis *et al* (2002) had demonstrated that the most important factor in obtaining an SVR was the hepatitis C genotype. Other predictors of response that had been shown to be more important than weight included baseline viral load, presence / absence of fibrosis and age.

Roche alleged that the phrase 'particularly weight' was therefore deliberately erroneous and misled the reader into believing bodyweight was the most important factor in obtaining an SVR and did not reflect the totality of current scientific opinion. Breaches of Clauses 7.2 and 7.4 were alleged.

RESPONSE

Schering-Plough stated that McHutchison *et al* and Poynard *et al* were among the earliest to introduce multivariate analysis to seek the independent predictive factors which influenced cure. These two investigators were amongst the leaders in searching for these predictive factors.

A review of the combined interferon alfa-2b monotherapy arms in both studies – total of 806 patients showed that 32% of patients < 55kg had a cure, 19% of patients 55-75kg, 13% of those 75-95kg and only 9% of the those > 95kg in weight respectively had a cure.

Schering-Plough would not dispute the point that there were other independent prognostic factors which were of equal, or greater, importance than weight. The figures on pages 3 and 4 of the booklet made this abundantly clear.

But as the title of this booklet made clear, it was about answering the question of whether weight was a prognostic factor. Therefore it could be assumed that the issue of weight was of particular importance to those individuals who read the booklet. In addition weight was unusual, of particular interest, in that it was the only independent parameter which was changed by the posology of the treatment. The phrase 'particularly weight' was certainly not deliberately erroneous, particularly considering the nature of the audience – specialists in hepatology.

Schering-Plough denied breaches of Clauses 7.2 and 7.4.

PANEL RULING

The Panel noted that McHutchison *et al* assessed the efficacy and safety of interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C and concluded that the combination treatment was more efficacious than monotherapy. The authors concluded that SVR was unrelated to age, sex, bodyweight or the estimated duration of disease. Pre-treatment variables known to influence the response to treatment were genotype, baseline serum HCV RNA level and the degree of fibrosis at baseline.

Poynard *et al* was a randomised trial which compared the safety and efficacy of interferon alpha-2b in combination with oral ribavirin administered for either 48 weeks or 24 weeks for treatment of chronic infection with hepatitis C virus. The study showed that in decreasing order of statistical significance the following were independent predictors of SVR; genotype 2 or 3, low baseline viral load, young age, low fibrosis stage and female sex. The authors concluded, *inter alia*, that a choice of regimen based on the number of response factors was probably more precise than a choice focussing only on virological characteristics. Weight was not mentioned as a predictive factor.

The Panel considered that the claim 'In the landmark studies published in the late 90s McHutchison and Poynard introduced the notion that factors such as genotype, age and particularly weight affected SVR outcomes' was inaccurate. McHutchison *et al* stated that SVR was unrelated to, *inter alia*, bodyweight and Poynard *et al* did not discuss weight as a predictive factor. The emphasis created by the use of the word 'particularly' was compounded by the section heading

'McHutchison and Poynard reported that weight is a predictive factor for response with fixed dose [interferon] alfa-2b monotherapy'. The claim was inaccurate, misleading and could not be substantiated; breaches of Clauses 7.2 and 7.4 were ruled.

3 Bodyweight

COMPLAINT

Roche stated that the continued focus of the booklet over-emphasised bodyweight as the main predictor of outcome in hepatitis C therapy and implied superiority of any interferon that was dosed by bodyweight (ie ViraferonPeg) over one that was a fixed dose (ie Pegasys). This was done, for example, by emboldened headlines: 'Zeuzem and Heathcote reported that weight is a predictive factor for response with fixed dose PEG-IFN [pegylated interferon] alfa-2a monotherapy' (Page 2).

There was no mention of bodyweight as a factor associated with outcome in Heathcote *et al* whilst in Zeuzem *et al* bodyweight was examined and found not to be a factor but body surface area was. This was misleading and the references inaccurate and a breach of Clauses 7.2 and 7.4 was alleged.

Roche referred to a number of claims in the booklet:

- 'Fried reports that weight is a predictive factor for SVR with fixed dose PEG-IFN alfa-2a plus ribavirin' (Page 4).
- 'The FDA analyses of the Hadziyannis study demonstrates that weight is a predictive factor for SVR with fixed dose PEG-IFN alfa-2a plus ribavirin' (Page 5).

and subsequently followed by the headline:

- 'Individualized therapy with weight adjusted PEG-IFN alfa-2b 1.5mcg/kg plus ribavirin >10.6mg/kg maximises the chance for an SVR in the broadest population of patients with HCV' (Page 8). [This claim appeared on page 12, not page 8 as stated by Roche. A similar claim 'Individualized weight adjusted PEG-IFN alfa-2b plus ribavirin therapy maximizes the chance for SVR in the broadest HCV population' appeared as a heading on page 8.].

and later the text:

- 'The analyses outlined in this document point to the fact that weight is a significant predictive factor for response when therapy is delivered as a fixed dose regimen. These analyses demonstrate that when therapy is delivered in a fixed dose regimen, larger patients demonstrate a lower SVR than do lighter patients. This suggests that larger patients may require a greater amount of drug to achieve an SVR than do lighter patients.

  The results reported in all the landmark trials suggest that weight adjusted therapy is necessary to maximise the chance for an SVR in the broadest population of patients with HCV' (Page 11).

And finally the document concluded:

– 'Individualized therapy with weight adjusted PEG-IFN alfa-2b 1.5mcg/kg plus ribavirin >10.6mg/kg maximises the chance for an SVR in the broadest population of patients with HCV by:
– Exerting a prolonged suppression of the virus
– Exerting a high level of specific activity (28% of the native interferon molecule)
– Ensuring that every patient receives the appropriate amount of both PEG-IFN alfa-2b µg/kg plus ribavirin to maximise the chances for an SVR' (Page 12).

Roche alleged that the initial headlines served to reduce confidence in Pegasys and disparage the product in breach of Clause 8.1, especially when put into context with the latter statements which exaggerated the efficacy of ViraferonPeg.

There was no prospective evidence to show that giving an increased dose of a fixed dose interferon (eg Pegasys) resulted in better response rates in heavier patients. Similarly there was no prospective evidence showing that results obtained with a weight-based dose of ViraferonPeg in combination with ribavirin (Manns *et al*) produced superior results to Pegasys used in combination with ribavirin (Fried *et al*).

Conversely the current evidence base showed that when both were compared to the same comparator (interferon alfa-2b and ribavirin) Pegasys and ribavirin was significantly more effective against patients with both genotypes 1 and non-1 and patients with both high and low viral loads, whilst the data with ViraferonPeg and ribavirin showed an improvement only in patients with genotype 1 and in patients with low viral loads.

Looking at subgroups of those patients with genotype 2/3, those patients with high viral loads and those with fibrosis/cirrhosis, there was no evidence to claim superiority in the 'broadest population of HCV patients'. Manns *et al* stated that the 'primary benefit of peginterferon alfa-2b plus ribavirin for this group (genotype 2/3) may be convenience, ease of administration of a once-weekly injection compared with alternate-day injections and the potential for better compliance' and again conflicted with the message of superiority in the 'broadest population of HCV patients' and 'maximises the chance for an SVR'. Therefore this was an exaggerated claim in breach of Clause 7.10.

The entire document over-emphasised the importance of weight in achieving an SVR and suggested that an interferon that was dosed by weight would not overcome this and so exaggerated the efficacy of ViraferonPeg whilst disparaging the clinical data on Pegasys. The evidence suggested that many factors were important in achieving an SVR in hepatitis C. Whilst weight was a factor in some studies, viral load, age and particularly genotype were more important.

The booklet suggested that an interferon dosed by bodyweight would stop weight being a predictor of outcome. However, prospective evidence showed that there was a decrease in SVR with an increase in bodyweight in studies with both Pegasys (Fried *et al* and Hadziyannis *et al*) and also ViraferonPeg (Manns *et al*).

The association of a decreased response with increased weight was confounded by a number of possible explanations, for example:

– increased steatosis (fatty liver) in patients who were heavier
– interferon resistance (as with insulin) in patients of a larger bodyweight
– sanctuary sites for hepatitis C
– an increase in alcohol consumption in larger patients.

Therefore, the intimation that dosing of an interferon by bodyweight overcame this was misleading and contrary to current evidence.

More disturbingly, Schering-Plough's frequent references to the FDA both in its written and verbal communications with health professionals attempted to legitimise the campaign which over-emphasised the importance of bodyweight in hepatitis C.

Whilst Roche understood from a previous case, Case AUTH1399/12/02, that Clause 9.4 [2001 edition] only referred to UK agencies Roche remained concerned that companies appeared to reference non-UK agencies as a way of supporting claims. In this way Schering-Plough appeared to be exploiting an apparent loop-hole in the Code.

Roche's concern was that this campaign could inadvertently lead to Pegasys being used outside the licensed dosing schedule to a regimen with unproven efficacy and safety. Therefore it asked that this booklet was withdrawn and recalled with immediate effect.

RESPONSE

Schering-Plough stated that Zeuzem *et al* found body surface area to be a prognostic factor. The text clearly stated in this section of the booklet that body surface area was being used as a surrogate for weight.

The Heathcote reference was inaccurate. Although Heathcote was co-author of the paper whose first author was Lee, which confirmed in a meta-analysis of trials with flat dosed pegylated interferon alfa-2a that weight was an independent prognostic factor, this point was not raised in the text of the article referenced. Schering-Plough accepted its error and would amend the version of the booklet under development.

The presented data demonstrated that ViraferonPeg and ribavirin, given in proportion to a patient's weight, removed weight from the list of independent prognostic variables for a cure. Pegasys used as licensed, did not. Schering-Plough submitted that the initial headlines were not disparaging.

Roche gave a list of reasons that could confound the association of a decreased response with increased weight, such as steatosis, interferon resistance, sanctuary sites, and increased alcohol consumption. This unreferenced, unsubstantiated theory was certainly worthy of further research, but was perhaps not completely relevant to the matter at hand.

The conclusions reached by this theorising, namely that 'dosing of an interferon by bodyweight overcame [the association of a decreased response with increased weight]' were refuted by the data given above.

Roche stated that its primary concern was that the campaign could inadvertently lead to Pegasys being used outside the licensed dosing schedule to a regimen with unproven efficacy and safety; this was certainly not Schering-Plough's intention and Roche's letter did not suggest how this would be likely to come about.

Schering-Plough stated that it had noted Roche's legitimate concerns and had, without waiting for the Panel's ruling, already taken steps to address them – as it would have, had Roche gone directly to Schering-Plough.

However, there seemed to be an attempt to use these specific issues to try to avoid the current consensus of medical opinion, namely that, irrespective of any other possible advantages of flat dosing with antiviral therapies in chronic hepatitis C, weight-based dosing with ViraferonPeg and ribavirin remained the only way currently available to remove weight as a prognostic factor.

PANEL RULING

The Panel noted that the emboldened headline 'Zeuzem and Heathcote reported that weight is a predictive factor for response with fixed dose PEG-IFN alfa-2a monotherapy' appeared within the section 'Monotherapy Trials with PEG-IFNs'. Subsequent text discussed data from the two trials.

Zeuzem *et al* compared the clinical effects of a regimen of peginterferon alfa-2a with interferon alfa-2a in the initial treatment of patients with chronic hepatitis C and showed that, *inter alia*, a smaller body-surface area independently and significantly ($p<0.001$) increased the odds of an SVR. Neither weight (> 85 vs ≤ 85kg) nor body-mass were similarly shown to affect response.

The Panel noted Schering Plough's submission that the reference to Heathcote *et al* in the headline claim at issue was incorrect; the correct reference was to Lee *et al*. Lee *et al* stated that baseline factors found to be independently predictive for SVR included bodyweight < 85kg. Table 2 of Lee *et al* gave independent factors associated with an SVR and included weight (< 85kg >; $p=0.0106$). Regression analysis was repeated for patients with genotype 1 whereby bodyweight was not given as a factor independently associated with an SVR. Among patients with genotype non-1, weight ≤ 85kg ($p=0.0050$) was given as a factor independently associated with SVR.

The Panel considered that the emboldened headline claim 'Zeuzem and Heathcote reported that weight is a predictive factor for response with fixed dose PEG-IFN alpha-2a monotherapy' was incorrect. Whilst subsequent text on the facing page and in a less prominent typeface presented some data from Zeuzem *et al* in relation to, *inter alia*, body surface area and described body surface area as a surrogate for weight it did not negate the overall impression created by the headline. The Panel further noted Schering-Plough accepted that the reference to Heathcote was incorrect. The Panel considered the claim misleading and not capable of substantation as alleged; breaches of Clauses 7.2 and 7.4 were ruled.

The Panel noted that ViraferonPeg was administered on a mcg/kg bodyweight basis. The licensed dose for

Pegasys was 180mcg as combination or monotherapy. The dose of ribavirin used in combination with Pegasys was dependent on the patient's weight.

The Panel noted that the headline claims 'Fried reports that weight is a predictive factor for SVR with fixed dose PEG-IFN alfa-2a plus ribavirin', 'The FDA analysis of the Hadzyiannis study demonstrates that weight is a predictive factor for SVR with fixed dose PEG-IFN alfa-2a plus ribavirin' and the penultimate paragraph on page 11 referred to by Roche which stated that '… weight is a significant predictive factor for response when therapy is delivered as a fixed dose regimen ...', concluding that 'larger patients may require a greater amount of drug to achieve an SVR than do lighter patients'.

The Panel considered that the individual and cumulative effect of such headline claims was to cast doubt upon the efficacy of the licensed dose for Pegasys. This was compounded further by the broad claims such as 'Individualized weight adjusted PEG-IFN alfa-2b plus ribavirin therapy maximizes the chance for SVR in the broadest HCV population' (page 8) and 'The results reported in all the landmark trials suggested that weight adjusted therapy is necessary to maximize the chance for an SVR in the broadest population of patients with HCV' (page 11). The Panel considered that the booklet was designed to disparage the licensed dosing regimen of Pegasys as alleged; a breach of Clause 8.1 was ruled.

The Panel noted that the claim 'Individualized weight adjusted PEG-IFN alfa-2b plus ribavirin therapy maximizes the chance for SVR in the broadest HCV population' appeared on page 8 and preceded a discussion about Manns *et al.* A similar claim 'Individualized therapy with weight adjusted PEG-IFN alfa-2b 1.5mg/kg plus ribavirin >10.6mg/kg maximizes the chance for an SVR in the broadest population of patients with HCV ...' appeared on page 12.

Manns *et al* assessed the efficacy and safety of two different regimens of peginterferon alfa-2b in combination with ribavirin compared with interferon alfa-2b plus ribavirin and identified predictors of response. The study showed that the most effective therapy was peginterferon alfa-2b 1.5mcg/kg per week in combination. This benefit was most apparent versus standard interferon therapy in patients with HCV genotype 1 infections. The study authors speculated that the primary benefit of peginterferon alfa-2b plus ribavirin in patients with HCV genotype 2 and 3 infections might be convenience, ease of administration of once a day dosing rather than alternative days and potential for better compliance. The HCV genotype (other than genotype 1), a low baseline viral load, lighter bodyweight and younger age were clearly associated with SVR ($p<0.0001$) as were gender and, to a lesser extent, the absence of cirrhosis. To assess the independence of these factors a further analysis was undertaken which showed that weight was still associated with SVR ($p=0.03$) but gender was no longer significant when weight was taken into account ($p=0.35$). The authors stated that secondary analysis identified bodyweight as an important predictor of SVR which prompted comparisons of the interferon regimens after adjusting ribavirin for bodyweight (mg/kg). After control for ribavirin dose (mg/kg) weight was no longer a significant predictor of response ($p=0.3$).

The Panel considered that the claim 'Individualised weight adjusted PEG-IFN alfa-2b plus ribavirin therapy maximizes the chance for SVR in the broadest HCV population' was not a fair reflection of the data in Mann *et al.* The benefit achieved with the most effective regimen of 1.5mcg/kg per week was achieved mainly in patients with types 2 and 3 genotype. Weight was not a significant independent predictor of response when control for ribavirin dose was taken into account. The claim exaggerated the data; a breach of Clause 7.10 was ruled.

B Market Research

COMPLAINT

Roche understood that provision of the booklet was followed up by a telephone call which would discuss the booklet and was described as 'Independent Research'. If this were to happen this would be disguised promotion in breach of Clause 10.2.

RESPONSE

Schering-Plough stated that the telephone call was not a follow-up sales call. As part of good marketing practice, the company periodically undertook what was known as detail follow up market research. This research was done in conjunction with an independent, professional market research agency. The purpose was to better help Schering-Plough understand the customer's perception of any particular message or product. This research enabled pharmaceutical companies to evaluate how and what was being communicated to their customers. Schering-Plough provided a copy of the questions that the market research agency developed as part of this detail follow up. No Schering-Plough personnel were affiliated with the research being done nor did the company know who the market research agency contacted.

PANEL RULING

The Panel noted the submission that the follow-up telephone calls were undertaken in conjunction with an independent market research agency. The company was not privy to whom the market research agency contacted. The Panel noted that the questionnaire was very detailed and covered product usage, the recollection of discussions on ViraferonPeg and the future prescribing intentions. The Panel noted Schering-Plough's submission that the questions were intended to help the company understand the customer's perception of any message or product. The Panel considered that the questions were designed to assist the company as stated rather than to promote ViraferonPeg as alleged. No breach of Clause 10.1 was ruled.

Complaint received **4 June 2003**

Case completed **22 August 2003**

CASE AUTH/1476/6/03

PROCTER & GAMBLE v LAGAP

Ipocol journal advertisement

Procter & Gamble alleged that a double-page journal advertisement issued by Lagap for Ipocol (enteric coated mesalazine 400mg), headed 'Mesalazine as a treatment for ulcerative colitis', with the sub-heading 'Ipocol and Asacol: New comparative data', implied that the products were essentially similar and this was misleading. Procter & Gamble supplied Asacol (enteric coated mesalazine 400mg).

Procter & Gamble noted that a generic product was regarded as being 'essentially similar' to an originator product where it 'satisfies the criteria of having the same qualitative and quantitative composition in terms of active substances, of having the same pharmaceutical form, and of being bioequivalent unless it is apparent in the light of scientific knowledge that it differs from the original product as regards safety and efficacy'.

There were strong indicators that Ipocol was not approved by the Medicines and Healthcare products Regulatory Agency (MHRA) as an 'essentially similar' product to Asacol: there were differences in the summaries of product characteristics (SPCs); Ipocol was approved with a proprietary name; MHRA policy on approval of modified release products and lack of bioequivalence data.

Procter & Gamble noted that the advertisement stated that 'Ipocol was designed to act like Asacol', followed by bullet points that tallied with the requirements for establishing essential similarity: 'Both products use Eudragit S in the tablet coating ...' (same qualitative composition); 'Both products can be described as mesalazine 400mg EC tablets …' (same quantitative composition in terms of active substance, same pharmaceutical form); 'Mesalazine was released and available *in vivo* by both products to a comparable extent (within ±20%) in a pharmacokinetic study' (implied bioequivalence).

Procter and Gamble stated that the data presented from a pharmacokinetic study in healthy volunteers implied that the two products were 'comparable', citing the ±20% limits that were routinely applied to assess the 'essential similarity' of two products. This was not a bioequivalence study. Additionally, it was not possible from the data on file provided by Lagap to evaluate the rigour of this study.

Procter & Gamble noted that, following publication of the advertisement in the Chemist & Druggist, a pharmacist wrote to the journal stating that they had been told that Ipocol was a generic version of Asacol. Procter & Gamble considered that Lagap's current advertising supported this message.

The Panel noted that 'essentially similar', in regulatory terms, was used to describe a generic equivalent of a branded product. The Panel did not consider that the readers would view the advertisement in those terms. In the Panel's view the advertisement did not portray Ipocol as a generic, interchangeable, version of Asacol. In that regard the Panel noted that the advertisement endorsed the practice of prescribing by brand. The Panel did not consider that the advertisement was misleading as alleged. There were some undeniable similarities between the products. No breach of the Code was ruled.

Procter & Gamble noted that Lagap concluded from *in vitro* dissolution data that 'a formulation that rapidly and extensively releases mesalazine above pH 7, like Ipocol, may confer benefits over a formulation that releases more slowly above this pH'. Procter & Gamble alleged that the implication that Ipocol had clinical benefits over Asacol was misleading.

The Panel noted that the advertisement was headed 'Mesalazine as a treatment for ulcerative colitis'. It appeared, therefore, that the advertisement related to the clinical use of mesalazine. Half of the first page however, referred to *in vitro* dissolution data and at one point a theoretical clinical advantage was noted for Ipocol. The Panel considered that undue emphasis had been given to *in vitro* data which might have no relevance to clinical efficacy. The Panel considered that the data presented suggested that Ipocol had clinical advantages over Asacol as alleged. A breach of the Code was ruled.

Procter and Gamble alleged that interim data from a clinical study cited in support and substantiation of the claim that 'there were no therapeutic differences' between Ipocol and Asacol was inadequate and unsuitable for that purpose.

The Panel noted that claim was referenced to data on file which had been provided by Procter & Gamble. No details were given of *inter alia* patient numbers, study design or statistical methods used. The Panel noted Lagap's submission that data had been restricted so as not to compromise the results of the study when completed. The Panel considered that the preliminary data released in the form of the data on file was so restricted that it was not sufficient to substantiate a claim of 'no therapeutic differences' between Ipocol and Asacol. A breach of the Code was ruled.

Procter & Gamble Pharmaceuticals UK, Limited complained about a double-page advertisement (ref 0244.010V2) for Ipocol (enteric coated mesalazine 400mg) issued by Lagap Pharmaceuticals Ltd. The advertisement was headed 'Mesalazine as a treatment for ulcerative colitis' with the sub-heading 'Ipocol and Asacol: New comparative data' and was presented in the style of an advertorial. The advertisement appeared in the pharmaceutical and medical press in May and June 2003. Procter & Gamble supplied Asacol (enteric coated mesalazine 400mg).

1 Implication of essential similarity

COMPLAINT

Procter & Gamble noted that the definition of 'essentially similar', ie generic products was: 'A medicinal product is essentially similar to an

originator product where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active substances, of having the same pharmaceutical form, and of being bioequivalent unless it is apparent in the light of scientific knowledge that it differs from the original product as regards safety and efficacy'.

The following points were strong indicators that Ipocol was not approved by the Medicines and Healthcare products Regulatory Agency (MHRA) as an 'essentially similar' product to Asacol, under Article 10 of 2001/83: there were differences in the summaries of product characteristics (SPCs); Ipocol was approved with a proprietary name; MHRA policy on approval of modified release products and lack of bioequivalence data.

Procter & Gamble noted that the advertisement stated that 'Ipocol was designed to act like Asacol', followed by bullet points that tallied with the requirements for establishing essential similarity;

- 'Both products use Eudragit S in the tablet coating ...' (same qualitative composition)
- 'Both products can be described as mesalazine 400mg EC tablets …' (same quantitative composition in terms of active substance, same pharmaceutical form)
- 'Mesalazine was released and available *in vivo* by both products to a comparable extent (within ±20%) in a pharmacokinetic study' (implied bioequivalence).

Procter and Gamble stated that the data presented from a pharmacokinetic study in healthy volunteers implied that the two products were 'comparable', citing the ±20% limits that were routinely applied to assess the 'essential similarity' of two products. This was not a bioequivalence study. Lagap had stated that 'a urinary excretion study was considered to be more relevant than a traditional bioequivalence study for this topically acting drug', however, this study design was not acceptable to European regulators to assess the similarity of modified release products. Additionally, it was not possible from the data on file provided by Lagap to evaluate the rigour of this study. A copy of the data on file was provided.

Procter & Gamble alleged that the implication that Ipocol tablets were essentially similar to Asacol tablets was misleading, in breach of Clause 7.2 of the Code.

Procter & Gamble noted that, following publication of the advertisement in the Chemist & Druggist, a pharmacist wrote, in the journal, that they had been told (by whom was not stated) that Ipocol and Asacol were therapeutically equivalent, ie Ipocol was a generic version of Asacol. Procter & Gamble considered that Lagap's current advertising supported this message and that the comments published in the Chemist & Druggist supported the company's argument that the advertisement was confusing health professionals.

Procter & Gamble noted that this same 'similarity' message was also conveyed in a 2 page insert, included in the Chemist & Druggist, that stated that 'Ipocol was designed to act like Asacol'.

RESPONSE

Lagap stated that it had presented the data available for Ipocol but had neither stated nor implied that the product was 'essentially similar' to Asacol. However, there were inevitably a number of similarities between the two products, since the Ipocol formulation was based on Asacol.

In development, certain minor adjustments were made to the Ipocol formulation to improve the consistency of release. The variability of release of mesalazine from Asacol tablets *in vitro* had been noted in studies by Lagap and by other investigators (Stolk *et al* 1990) and it was considered that this could be improved upon. The key ingredient that mediated the release of the mesalazine, Eudragit S, remained the same in both products.

When referring to mesalazine products it would be inappropriate not to mention this coating/release mechanism. Since both Ipocol and Asacol contained Eudragit S in the tablet coating, this was what the advertisement must state.

Lagap noted that the description of the quantitative composition of the product was within a section of the advertisement discussing the various mesalazine products on the market and was comparing and contrasting the characteristics of all of them. The similarities between Ipocol and Asacol warranted that they be included within the same paragraph and in such a way so as not to repeat the information, the other mesalazine products with differing doses and formulation characteristics were then dealt with in the following paragraph.

Lagap considered it important to highlight to readers that both products contained Eudragit S, to counteract the confusion caused by a letter sent to doctors, by a third party, last October. This letter contained a table comparing the features of the various mesalazine products. Asacol was described as using 'Eudragit S coating', whilst Ipocol used a 'polymer resin coating'. This misled readers into assuming that the two coatings were completely different.

With regard to the pharmacokinetic study, Lagap considered that providing a measure on which the term 'comparable' was based was more transparent than just stating that the two products were comparable.

Lagap noted that community pharmacists, the intended audience of the advertisement in question, would not know about the regulatory requirements for establishing essential similarity and would not, unlike Procter & Gamble, be looking at the material with the aim of finding anything that could be potentially linked to an imagined claim of 'essential similarity'.

Lagap stated that since Ipocol was designed to act like Asacol and had a very similar formulation it was not surprising that the weight of evidence would reflect the similarities between the two products. There was nothing implied in this – it was just a reflection of the available data – and use of the most suitable word to describe the relationship between the two products.

Despite the numerous similarities, the fact that the two products were not identical was recognised and

the advertisement ended with a recommendation that patients were not continually swapped between brands.

PANEL RULING

The Panel noted that according to the advertisement new comparative data on Ipocol and Asacol were presented. Following a brief description of ulcerative colitis the advertisement included an overview of the different forms of mesalazine available. Ipocol and Asacol were discussed in the same paragraph. It was stated that both contained 400mg of mesalazine in a tablet coated with Eudragit S and that the dosage regimen for ulcerative colitis was the same for both products. *In vitro* data was presented which showed that the dissolution characteristics of Ipocol and Asacol were similar. A healthy volunteer study showed that the pharmacokinetics of the two products was comparable and it was stated that interim results from a clinical study demonstrated no therapeutic differences. The penultimate paragraph of the advertisement stated that 'Ipocol is very similar to Asacol'.

The Panel noted that 'essentially similar', in regulatory terms, was used to describe a generic equivalent of a branded product. The Panel did not consider that the readers would view the advertisement in those terms. In the Panel's view the advertisement did not portray Ipocol as a generic, interchangeable, version of Asacol. In that regard the Panel noted that the advertisement endorsed the practice of prescribing by brand. The Panel did not consider that the advertisement was misleading as alleged. There were some undeniable similarities between the products. No breach of Clause 7.2 was ruled.

2 *In vitro* comparative dissolution data

COMPLAINT

Procter & Gamble noted that Lagap concluded from *in vitro* dissolution data that 'a formulation that rapidly and extensively releases mesalazine above pH 7, like Ipocol, may confer benefits over a formulation that releases more slowly above this pH'. Procter & Gamble considered that to extrapolate *in vitro* data to state that Ipocol 'confers benefits' over another formulation was in breach of Clause 7.2. Although this paragraph concluded with a statement that further *in vivo* investigation would be needed to assess 'behaviour in the clinic', this did not negate the misleading implication that the *in vitro* data presented suggested that Ipocol had clinical 'benefits' over Asacol.

RESPONSE

Lagap stated that it had clearly presented the data and made an observation. The statement at issue actually read '**Theoretically** a formulation ….. **may** confer benefits on a formulation that releases more slowly above this pH' (emphasis added).

As noted by Procter & Gamble this statement was followed by 'Specific studies in man would be required to relate these *in vitro* differences between Ipocol and Asacol to their behaviour in the clinic'. In addition, this section on *in vitro* data began with a paragraph highlighting that 'There is currently no evidence of any direct correlation between dissolution data and the behaviour of mesalazine in man'.

With all the caveats and qualifications as to the limitations of *in vitro* data, Lagap did not accept that the statement at issue could be construed as misleading.

Lagap considered that *in vivo* data and clinical experience were far more relevant to the clinical use of a medicine than *in vitro* data. This was why dissolution data had not been included in any of the earlier standard medical information responses on Ipocol. The only reason for including the comparative dissolution study in this advertisement was again to respond to a third party's comparative *in vitro* data that had been widely circulated over the previous months.

These comparative *in vitro* data were accompanied by comments highlighting that Ipocol had a 'significantly different *in vitro* dissolution profile' to Asacol (or similar statements), using these findings to imply that the behaviour of the two products in man would be different. Other associated comments had included 'the dissolution profile of a mesalazine formulation mediates the site of release'.

Whilst such comments might be appropriate in situations where there were data to show that the *in vitro* data were of direct relevance, this was not the case for mesalazine. This had not been made clear in any of the publications or letters including these data that Lagap had seen.

Lagap stated that the majority of community pharmacists would have little or no knowledge of dissolution data and its relevance or otherwise in man. Lagap therefore considered it was important to highlight to them the limitations of *in vitro* data, whilst presenting new data that differed in some key aspects from that previously described.

PANEL RULING

The Panel noted that the advertisement was headed 'Mesalazine as a treatment for ulcerative colitis'. It appeared, therefore, that the advertisement related to the clinical use of mesalazine. Half of the first page however, referred to *in vitro* dissolution data and at one point a theoretical clinical advantage was noted for Ipocol. Although the part of the advertisement which referred to dissolution data started with the sentence 'There is currently no evidence of any direct correlation between dissolution data and the behaviour of mesalazine in man' and ended with 'Specific studies in man would be required to relate these *in vitro* differences between Ipocol and Asacol to their behaviour in the clinic' the Panel nonetheless considered that undue emphasis had been given to *in vitro* data which might have no relevance to clinical efficacy. The Panel considered that despite the caveats the data presented suggested that Ipocol had clinical advantages over Asacol as alleged. A breach of Clause 7.2 was ruled.

3 Comparative clinical data

COMPLAINT

Procter and Gamble alleged that the presentation of interim data from a clinical study was in breach of Clause 7.4 in that the study relied upon to support and substantiate the claim that 'there were no therapeutic differences' between Ipocol and Asacol was inadequate and unsuitable for that purpose.

The data on file provided by Lagap included limited data on this interim analysis, which did not provide sufficient information to allow assessment of the strength of this study. No results were provided (delta, confidence intervals, type of statistical evaluation performed). There was no information on study design (blinded or not, intended to demonstrate non-inferiority or equivalence), number of patients, baseline demographics (eg severity, extent or site of disease), study duration, timepoint of primary endpoint evaluation, primary endpoint success criteria (was the 'modified' St Mark's score a validated assessment tool, and what score, or change in score was considered a successful outcome).

RESPONSE

Lagap stated that it aimed to provide a comprehensive overview of the available data on Ipocol in the advertisement. That was why the comparative clinical study was included. It was clearly stated that these were interim data. Limited data were provided as the trial was ongoing and remained blinded. It was therefore considered appropriate to restrict the information released at this stage so as not to compromise the overall results of the study, when completed.

PANEL RULING

The Panel noted that the advertisement referred to interim data from a clinical study comparing Asacol and Ipocol which indicated no therapeutic differences between the two. The claim was referenced to data on file. Procter & Gamble had provided a copy of the relevant data on file which consisted of six short paragraphs describing the study. No details were given of *inter alia* patient numbers, study design or statistical methods used. The Panel noted Lagap's submission that it had released some of the data so as to provide a comprehensive overview but that that data had been restricted so as not to compromise the results of the study when completed. The Panel considered that the preliminary data released in the form of the data on file was so restricted that it was not sufficient to substantiate a claim of 'no therapeutic differences' between Ipocol and Asacol. A breach of Clause 7.4 was ruled.

Complaint received **6 June 2003**

Case completed **13 August 2003**

PRIMARY CARE TRUST PHARMACIST v PROCTER & GAMBLE

Asacol MR journal advertisement

A primary care trust pharmacist complained that a journal advertisement for Asacol MR (modified release mesalazine) issued by Procter & Gamble was misleading as it directly inferred that Asacol was a modified release preparation both in the body of the advertisement and in the prescribing information.

In the complainant's view, unless Procter & Gamble had licensed a new mesalazine product that was a modified release product, the advertisement was misleading and inappropriate.

The Panel noted that the Asacol MR summary of product characteristics (SPC), last updated in April 2003, described the product as being in the form of 'red-brown, oblong, modified release tablets'. The Panel therefore did not consider that it was either misleading or inappropriate to refer to Asacol MR as being a modified release preparation. No breaches of the Code were ruled.

A primary care trust pharmacist complained about a journal advertisement (ref AS2131 May 2003) for Asacol MR (modified release mesalazine) issued by Procter & Gamble Pharmaceuticals UK, Limited. The advertisement read 'If you prescribe oral mesalazines generically … you can't be sure that your patients will get the therapy you intend'. A quotation from MeReC Bulletin 11(4), 2000 read 'it seems sensible to recommend brand name prescribing for modified release preparations'. Prescribing information for Asacol MR appeared at the bottom of the advertisement.

COMPLAINT

The complainant stated that the advertisement drew attention to the differences that had been demonstrated *in vitro* between two brands of mesalazine 400mg enteric coated tablets, namely Asacol and Ipocol. The complainant alleged that the advertisement was misleading as it directly inferred that Asacol was a modified release preparation both in the body of the advertisement with the reference to a MeReC Bulletin, and in the prescribing information. In the complainant's view, unless Procter & Gamble had licensed a new mesalazine product that was a modified release product, the advertisement was entirely misleading and totally inappropriate.

The Authority asked Procter & Gamble to respond in relation to Clauses 7.2, 7.3 and 7.4 of the Code.

RESPONSE

Procter & Gamble noted that the complainant was concerned that Asacol was being incorrectly portrayed as a modified release product, when in fact (s)he believed the pharmaceutical form to be enteric coated. The pharmaceutical form of Asacol, taken from the summary of product characteristics (SPC) was 'modified release'. The company therefore denied a breach of the Code.

The pharmaceutical form descriptor for Asacol tablets was recently updated in order to comply with current guidelines on terminology (European Directorate for the Quality of Medicines, Standard Terms, December 2002) and to better reflect the release characteristics of the product. There had been no change to the product itself, only to the terminology used.

PANEL RULING

The Panel noted that Section 3 of the Asacol MR SPC (last updated in April 2003) described the product as being in the form of 'red-brown, oblong, modified release tablets'. The Panel therefore did not consider that it was either misleading or inappropriate to refer to Asacol MR as being a modified release preparation. No breach of Clauses 7.2, 7.3 and 7.4 was ruled.

Complaint received **13 June 2003**

Case completed **7 August 2003**

MEDIA/DIRECTOR v ROCHE

Anti-obesity campaign

A Sunday Herald article entitled 'Drug firm's obesity 'advert' should be banned, say GPs', stated that a campaign run by Roche to raise public awareness of the health risks of obesity was in breach of advertising rules and should be withdrawn immediately. The article stated that doctors believed the campaign was an elaborate form of direct to patient advertising. In accordance with established procedure, the matter was taken up by the director as a complaint under the Code.

Roche supplied Xenical (orlistat) which was licensed for use, in conjunction with diet, for the treatment of obese or overweight patients with associated risk factors.

Roche provided copies of two advertisements that had appeared in the lay press in mid to late June. One which showed a picture of a portion of unwrapped fish and chips had the headline 'Trying to lose weight? We can make temptation old news' and the other, which depicted a belt on which the wearer had had to use the last holes, incorporated the headline 'Is your weight loss plan not working?'. Each advertisement told readers that if they were serious and needed to lose a stone or two, help was at hand. For 'free information on better health and weight loss success' readers could return a coupon or use a freephone number.

Surgery posters featured the photograph of the belt and the headline 'Is your weight loss plan not working?'. Readers were told that being overweight could cause serious long-term health problems and that as with other health issues they could get advice from their doctor or pharmacist. Readers were invited to take a leaflet and 'make it happen'.

The Panel noted that the belt picture and headline were on the front cover of the leaflet. Readers were told that they were not alone and that almost half the adults in the UK had a problem with their weight. Some of the implications of being overweight were listed. Under a headline of 'Your doctor can really help' readers were told that if they'd previously been unsuccessful in losing weight and keeping it off, their doctor would be able to help. In addition to providing advice the doctor could now also prescribe effective treatments if appropriate. Such treatments were not miracle cures but they could make a big difference if combined with eating and exercise plans. Readers were told that some of the treatments also involved free support programmes which could be a big help and that their doctor could only prescribe a weight loss treatment if they were considered to be medically overweight. The final page of the leaflet told readers that one of the best ways to lose weight was to reduce fat intake and that increased exercise was another good way but that if they were still finding it hard '… there is more you can do in addition to lifestyle changes'.

The Panel considered that the materials provided encouraged people who had tried to lose weight, but failed, to seek medical help but did not encourage them to ask for a specific medicine. It was for the GP to decide whether treatment was appropriate and if so what treatment would be recommended. All of the written materials provided included the Roche company logo and the statement 'Health education sponsored by Roche Products Limited'. The Panel did not consider that the materials amounted to an advertisement to the general public for Xenical or that they would encourage patients to ask their doctors to prescribe Xenical. No breaches of the Code were ruled.

An article entitled 'Drug firm's obesity 'advert' should be banned, say GPs' in the Sunday Herald, 15 June, was critical of a campaign run by Roche Products Limited to raise awareness of obesity. Roche supplied Xenical (orlistat) which was licensed for use, in conjunction with diet, for the treatment of obese or overweight patients with associated risk factors. In accordance with established procedure, the matter was taken up by the Director as a complaint under the Code.

COMPLAINT

The article stated that a campaign by Roche to raise public awareness of the health risks of carrying excess weight was in breach of advertising rules and should be withdrawn immediately. The article stated that doctors believed the campaign was an elaborate form of direct to patient advertising. The advertisements included the Roche logo and stated 'Trying to lose weight? We can make temptation old news'. Patients were invited to send for more information or call a Freephone telephone number.

When writing to Roche the Authority asked it to respond in relation to Clauses 2, 9.1, 9.9, 20.1 and 20.2 of the Code (2001 edition).

RESPONSE

Roche contested absolutely that it had, in any way, breached the Code. Roche believed that the doctors commenting in the article were ill-informed and the article appeared to have been subject to inappropriate sub-editing.

The aim of the disease awareness programme was to provide high quality information to the general public about a disease that currently affected one in five adults in Scotland, had an increasing prevalence and caused a great deal of ill health and excessive health expenditure in Scotland. Ultimately, Roche hoped to see a similar campaign run in the rest of the UK. The disease awareness campaign contained no direct or indirect mention of Xenical but was run with the endorsement of the National Obesity Forum, in an attempt to empower the public to make informed decisions about their health, including whether to visit a health professional should they believe their weight was a problem. The programme was developed over the past year and Roche had kept the Scottish Executive health department informed throughout the process. Indeed, patients with a

health enquiry were directed towards their NHS Helpline in the documentation.

Prior to the publication of the advertisements in the Scottish press, all GPs and pharmacists were informed by letter of the impending programme. Surgery posters and leaflets were made available to 200 pharmacies and all primary care surgeries in Scotland. Copies of all the materials which comprised this campaign were provided. As required by Clause 9.10 of the 2003 edition of the Code, the Roche logo was included to indicate that the company had sponsored the campaign.

Roche did not accept that Clauses 2, 9 or 20 or indeed any other clauses of the Code had been breached.

PANEL RULING

The Panel considered that patient education programmes about a disease area were a legitimate activity for a pharmaceutical company to undertake. Such activity had to comply with the Code. Although disease awareness campaigns might facilitate the market development of the sponsoring company's product this was not necessarily in breach of the Code. Each case would need to be judged on its merits.

The Panel noted the definition of promotion given in Clause 1.2 excluded statements relating to human health or disease providing there was no reference, either direct or indirect, to specific medicines. The Panel noted that Clause 20.1 prohibited the advertising of prescription only medicines and certain other medicines to the general public. Clause 20.2 of the Code permitted information to be supplied directly or indirectly to the general public but such information had to be factual and presented in a balanced way. It must not raise unfounded hopes of successful treatment or be misleading with respect to the safety of the product. Statements must not be made for the purpose of encouraging members of the public to ask their doctor to prescribe a specific medicine.

Roche had provided copies of the two advertisements which had appeared in the Scottish lay press in mid to late June. One showed a picture of a portion of unwrapped fish and chips and had the headline 'Trying to lose weight? We can make temptation old news', and the other, which depicted a belt on which the wearer had had to use the last holes, incorporated the headline 'Is your weight loss plan not working?' Each advertisement told readers that if they were serious and needed to lose a stone or two, help was at hand. For 'free information on better health and weight loss success' readers could return a coupon or use a Freephone number.

No transcript of the Freephone number helpline was provided. On ringing in late July, a message was given that the service had been suspended. Previously the helpline had included some information about weight loss and an invitation for callers to give their details to receive a leaflet.

Surgery posters featured the photograph of the belt and the headline 'Is your weight loss plan not working?'. Readers were told that being overweight could cause serious long-term health problems and that as with other health issues they could get advice from their doctor or pharmacist. Readers were invited to take a leaflet and 'make it happen'.

The belt picture and headline were on the front cover of the leaflet. Readers were told that they were not alone and that almost half the adults in the UK had a problem with their weight. Some of the implications of being overweight were listed. Under a headline of 'Your doctor can really help' readers were told that it they'd previously been unsuccessful in losing weight and keeping it off, their doctor would be able to help. In addition to providing advice the doctor could now also prescribe effective treatments if appropriate. Such treatments were not miracle cures but they could make a big difference if combined with eating and exercise plans. Readers were told that some of the treatments also involved free support programmes which could be a big help. Readers were further told that their doctor could only prescribe a weight loss treatment if they were considered to be medically overweight. A chart was provided so that readers could determine, from their height and weight, if they were medically overweight. The final page of the leaflet told readers that one of the best ways to lose weight was to reduce fat intake and that increased exercise was another good way but that if they were still finding it hard '… there is more you can do in addition to lifestyle changes'.

The Panel considered that the materials provided encouraged people who had tried to lose weight, but failed, to seek medical help but did not encourage them to ask for a specific medicine. It was for the GP to decide whether treatment was appropriate and if so what treatment would be recommended. All of the written materials provided included the Roche company logo and the statement 'Health education sponsored by Roche Products Limited'. No breach of Clause 9.9 (2001 edition of the Code) was ruled. The Panel did not consider that the materials amounted to an advertisement to the general public for Xenical. No breach of Clause 20.1 was ruled. The Panel also did not consider that the materials would encourage patients to ask their doctors to prescribe Xenical and so ruled no breach of Clause 20.2 of the Code. The Panel ruled no breach of Clause 9.1 of the Code and thus no breach of Clause 2 of the Code.

Proceedings commenced **19 June 2003**

Case completed **13 August 2003**

CASE AUTH/1481/6/03

PROFILE PHARMA v FOREST LABORATORIES

Promotion of Colomycin

Profile Pharma alleged that Forest Laboratories had promoted the 2MU vial of Colomycin at a European Congress, held in Belfast, before the product had been granted its marketing authorization. Materials featuring the picture of a vial with '2MU' on it had been displayed for the whole of the conference period (3-7 June) although the marketing authorization had not been granted until 6 June. Profile alleged that promotion of the new product constituted teaser advertising, as the product was unavailable, and was offensive to the professional standing of the delegates. Profile also alleged a breach of Clause 2 of the Code.

The Panel noted that although the main scientific meeting did not start until 5 June, the day on which the marketing authorization for Colomycin 2MU was granted, company stands were set up (as requested by the organisers) on the previous afternoon. Material referring to the 2MU presentation would thus have been seen by delegates who attended, *inter alia*, the opening ceremony and reception on 4 June. The Panel considered that Forest Laboratories had promoted the product prior to the grant of a marketing authorization. A breach of the Code was ruled. The Panel did not consider that the advertising constituted teaser advertising and no breach of the Code was ruled in that regard. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 of the Code.

Profile Pharma Ltd complained about the promotion of Colomycin Injection by Forest Laboratories UK Limited.

Colomycin was presented in vials each containing 500,000, 1,000,000 or 2,000,000 units of colistimethate sodium. The vial containing 2,000,000 units (2MU) was listed on the summary of product characteristics (SPC) as being approved in June 2003.

COMPLAINT

Profile alleged that Forest Laboratories had promoted an unlicensed medicine at the European Cystic Fibrosis Congress held in Belfast, 3 to 7 June 2003. Forest Laboratories was the main sponsor of the meeting.

Profile stated that promotional materials for a new 2MU presentation of Colomycin Injection were extremely prominent at the meeting. These being large posters of a vial with '2MU' and Forest Laboratories' logo on it; the delegates' bag contained a flyer mentioning the 'Internet Café' sponsored by Forest Laboratories but the dominant visual was a picture of a vial with '2MU' on it; on approaching the Forest Laboratories stand delegates saw a large display spread over 3 exhibition panels. The middle panel was a reproduction of a vial with '2MU' on it. The panels on either side referred to promotion of Forest Laboratories' authorized product Colomycin. The juxtaposition of the Colomycin promotion and the picture of a vial with '2MU' on it clearly implied that the new product was available.

All of the representatives manning the Forest Laboratories stand were dressed in polo shirts with a picture of a vial with '2MU' and inside the building all the posters directing delegates to the 'Internet Café' featured a vial with '2MU'.

The items were displayed for the whole of the conference period (3 to 7 June). Profile stated that the marketing authorization for the new product was only granted on 6 June.

Profile stated that the generality of Forest Laboratories' activities at the meeting and in particular the advertising on Forest Laboratories' stand were promotional and inferred that the new product was available. Accordingly it concluded that during 3 to 5 June 2003 Forest Laboratories promoted the new product despite the fact that it was not authorized. A breach of Clause 3.1 of the Code was alleged.

Profile further alleged that the promotion of the new product constituted teaser advertising inducing delegates to inquire about it. Upon enquiry, delegates were advised that no information was available until the following week when the new product would be in the wholesalers. A breach of Clause 9.1 was alleged as the promotion was offensive to the professional standing of the delegates in that it sought to elicit '… an interest in something which will be following or will be available at a later date without providing any actual information about it'.

Profile also alleged a breach of Clause 2 of the Code.

RESPONSE

Forest Laboratories submitted that at no time during its attendance at the European Cystic Fibrosis Congress was an unlicensed product promoted.

The marketing authorization for the 2MU presentation of Colomycin Injection was granted on 5 June 2003. Forest Laboratories was aware before attending the Belfast meeting that a licence had been granted but as a precaution, in case the necessary documentation was not received in time for the meeting, an alternative set of exhibition panels were taken. In the event it was not necessary to use the alternative campaign. No literature promoting the 2MU presentation of Colomycin was used prior to 5 June 2003.

The European Congress Opening Ceremony was held on Wednesday 4 June at 5.30pm. Registration commenced on Thursday 5 June at 7am, the first plenary session commenced at 8.30am. A copy of the scientific programme was provided.

On Wednesday afternoon (as requested by the organisers) the stand was set up ready for the start of the clinical sessions on Thursday morning. The Forest Laboratories representatives arrived at 8am on the Thursday to staff the stand.

PANEL RULING

The Panel noted that according to the scientific programme registration for the meeting opened on Wednesday 4 June with meetings of various groups. The opening ceremony was between 5.30pm and 7pm followed by a reception. The main scientific meeting commenced on Thursday 5 June.

The Panel noted that the marketing authorization for the 2MU presentation was dated 5 June. It considered that as material referring to the 2MU presentation was displayed on 4 June and would be seen to delegates who attended the meeting on that day, Forest Laboratories had thus promoted the product prior to the grant of the marketing authorization. A breach of Clause 3.1 of the Code was ruled with regard to the printed promotional material referred to by Profile.

The Panel did not consider that the advertising constituted teaser advertising as it was obvious that Forest Laboratories was promoting the 2MU dose of its product. No breach of Clause 9.1 of the Code was ruled.

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

Complaint received **19 June 2003**

Case completed **22 August 2003**

CASE AUTH/1482/6/03

CONSULTANT PHYSICIAN v AVENTIS PHARMA

Conduct of representative

A consultant physician complained about the promotion of Lantus (insulin glargine) by Aventis Pharma. The complainant stated that an Aventis representative had told her about the Insulin for Life Programme and said that he had discussed the programme in detail with two consultant physicians who were her colleagues and that they were in agreement with it. One of her colleagues had told the complainant that he had not expressed a view on the programme and the other had only had a conversation in the corridor with the representative. He had not received any detail of the programme and had certainly not expressed approval or support.

At a subsequent meeting of diabetes specialist nurses, the representative had again discussed the programme and had inferred that the complainant and her colleagues knew about it and were in agreement with it. That was not the case.

The Panel considered that the representative had misrepresented the views of the two consultants. Although he had had a formal meeting with one he had only met the other in the corridor. There had been no meeting between the two consultants and the representative for almost three months when he had met the complainant. From the information before it the Panel considered that the representative's statement that the programme was 'currently under discussion' was not a fair reflection of the situation. The complainant had been given the impression that her colleagues 'were in agreement with the plan' which was not so. The Panel considered that the representative had failed to maintain a high standard of ethical conduct and breaches of the Code were ruled.

The Panel noted that shortly after having spoken to the complainant, the representative had been at a meeting of diabetes specialist nurses. Aventis submitted that in response to a question about the degree of local support for the programme, the representative had referred to his earlier discussions with the two consultants; he did not state or imply that the three consultants were united in their support as he knew that he had not sought the views of the complainant. The complainant submitted that he had used her name and those of her two colleagues and implied that all three were in agreement with the project. Notwithstanding the use or not of the complainant's name, the Panel considered that reference to the discussions with the other two consultants would positively influence the nurses and lead them to assume that the consultants favoured the programme. In the circumstances the Panel did not consider that it was adequate for the representative not to state that the consultants supported the programme; the representative should have stated unequivocally that they had not yet either approved or disapproved of the programme. Failure to explain the situation accurately would lead to the nurses drawing their own conclusions. The Panel considered that the representative had failed to maintain a high standard of ethical conduct and further breaches of the Code were ruled.

A consultant physician complained about the promotion of Lantus (insulin glargine) by Aventis Pharma Ltd.

COMPLAINT

The complainant stated that she was approached by an Aventis representative at a joint meeting of the local Diabetes Groups on 7 May. The representative told the complainant about a study which Aventis was doing although at that time he gave no clinical information. He told the complainant that he had discussed these plans in detail with two other consultant physicians and that they were in agreement with the plan, and that she 'was the only person he had not yet managed to speak to'. The complainant explained to the representative that there was a system of departmental lunch time meetings for disseminating information and that he should approach the diabetes secretaries to arrange such a meeting if he wished to. The complainant was later

told by the two consultants that they had not been approached by the representative or been involved in discussions about this study involving Lantus.

The complainant stated that a few days later the diabetes sister at her hospital was at a local meeting for diabetes specialist nurses at which the representative was also present. The complainant was told that he again discussed the proposal that Aventis would train general practitioners' practice nurses to put patients onto Lantus on the understanding that ten patients per practice would be recruited. Again he used the names of the complainant and her colleagues in association with this project, with the implication that all were in agreement with it and knew about it. This was not the case.

These matters were of great concern to the complainant personally and to the local diabetes group.

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

RESPONSE

Aventis explained that its Insulin for Life Programme, which the complainant had clearly misunderstood and referred to as a 'study' was a two part programme of education and practical support. Details were provided. Aventis was confident that the programme maintained the expected high standards of the industry and neither constituted disguised promotion nor an inducement to prescribe Lantus or any other Aventis product. Aventis considered that the Insulin for Life Programme adhered to the Code and was not in breach of any clause, but notably Clauses 2, 9.1, 10.2 nor 18.1.

Aventis stated that it fully understood that diabetes care was integrated across primary and secondary care boundaries and that all interested parties must be fully informed about the invitation to participate in such a healthcare support programme in order that their opinions were sought and recognised. To this end Aventis' representatives took great care to fully discuss the Insulin for Life Programme with both primary care organisations and hospital diabetes units to ensure the programme was supported in each area in which it was made available. Several written materials were available to support them in achieving this.

The representative concerned was experienced and had passed the ABPI examination. He knew that he needed to introduce the programme to the consultant physicians at the diabetes unit. With this in mind, a meeting was scheduled and held with one of them on 17 February. The consultant's views were interpreted as being positive and some synergies were identified between the programme and the work that he was already undertaking with primary care colleagues in the locality. On the same visit an informal conversation occurred with the other consultant at which the programme and the earlier discussion with the other consultant was mentioned, though not in the same level of detail.

The chance meeting with the complainant on 7 May gave the representative the opportunity to mention that the programme was currently under discussion and to pass on his contact details. The complainant outlined how a formal meeting could be scheduled if necessary in the future. The content of the programme was not discussed and undoubtedly this explained the subsequent misunderstanding as regards the detail, which was evident in the complaint.

At the subsequent local diabetes specialist nurse meeting, the programme was outlined by the representative. In response to a question about the degree of support of local hospital clinicians, he recalled having mentioned his earlier discussions with the two consultants. However he neither actively stated nor intimated that all three physicians were united in their support, as he fully recognised that he had not solicited the views of the complainant.

It was clear from subsequent discussions with the three local healthcare co-operatives that the programme was not of current interest in the area at this time. Thus no formal meeting had been scheduled with the local hospital consultants to follow the matter up, as no further consultation was required.

In conclusion, Aventis stated that it was clear that the complainant had formed an inaccurate view of the programme. It was also regrettable that the diabetes sister left the diabetes specialist nurse meeting with the impression that all of the local hospital consultants supported the programme. It was most certainly not the representative's intention to create this impression as he recognised that this conclusion had not been reached.

Aventis was wholly satisfied that the activities of its representatives in attempting to inform all the diabetes stakeholders in the area about the programme were carried out to the high standard of ethical conduct that Aventis strove to maintain. Aventis denied any breach of the Code.

* * * * *

Aventis' response was sent to the complainant for comment.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant noted that Aventis' response did not change her complaint which was about misrepresentation. The complainant made further comments about the Insulin for Life Programme.

Turning to the issue of misrepresentation, the complainant stated that she had spoken again with her colleague regarding the meeting he had with the representative on 17 February. During this meeting the representative outlined the Insulin for Life Programme; her colleague told the complainant that he did not express a view on the programme itself. Her other colleague also remembered being introduced to the representative that day. That conversation took place in the corridor. He told the complainant that he did not receive any detail of the Insulin for Life Programme, and certainly did not express approval or support.

The complainant alleged that the representative misrepresented the views of her colleagues to her, when he approached her on 7 May. He clearly

implied that they were both fully informed of the programme. The complainant noted that she worked in a small department within which information was readily shared and therefore she was surprised (had this been the case) that neither of her colleagues had mentioned it to her. The complainant stated that she expressed this surprise to the representative at the time, and explained how a formal departmental meeting could be arranged.

The complainant stated that she had spoken to two people who had attended the diabetes specialist nurse meeting and both remembered the representative stating that he had spoken to all of the local consultants, including the complainant. This statement was of course true in essence, but it was made in response to a question posed about the degree of support for the programme. The complainant considered that by answering the question in this way there was a deliberate implication that the consultants were in support. In a speciality like diabetes, where clinical decisions were traditionally led by secondary care, it would be extremely difficult to popularise a programme in primary care which did not have the full support of the local hospital consultants.

PANEL RULING

The Panel noted that the complainant was concerned that with regard to the Insulin for Life Programme, the representative had misrepresented the views of two of her colleagues to her and had also misrepresented the views of all three doctors to diabetes specialist nurses at a meeting.

The Panel noted that in February the representative had held a formal meeting with one of the consultants. The company submitted that his views were interpreted as being positive and some synergies were identified between the programme and the work that he was already undertaking with primary care colleagues in the locality. On the same day an informal conversation occurred with another consultant at which the programme and the earlier discussion with one of her colleagues were mentioned although not in the same level of detail. The complainant submitted that the first of her colleagues had not expressed a view on the programme itself and that the meeting with the other had taken place in a corridor. Nearly 3 months later, with apparently no other meetings with either consultant in the meantime, the representative had had a chance meeting with the complainant. Aventis submitted that that meeting gave the representative the opportunity to mention that the programme was currently under discussion and to pass on his contact details. The content of the programme was not discussed with the complainant. The complainant stated that the representative had told her that he had discussed the plans in detail with her two colleagues.

The Panel considered that the representative had misrepresented the views of the two consultants. Although he had had a formal meeting with one he had only met the other in the corridor. There had been no meeting between the two consultants and the representative for almost 3 months when the representative had met the complainant. From the information before it the Panel considered that the representative's statement that the programme was 'currently under discussion' was not a fair reflection of the situation. The complainant had been given the impression that her colleagues 'were in agreement with the plan' which was not so. The Panel considered that the representative had failed to maintain a high standard of ethical conduct and breaches of Clauses 9.1 and 15.2 were ruled.

The Panel noted that shortly after having spoken to the complainant, the representative had been present at a meeting of diabetes specialist nurses. Aventis submitted that in response to a question about the degree of support for the programme from local consultants, the representative had referred to his earlier discussions with the two consultants; he did not state or imply that the three consultants were united in their support as he knew that he had not sought the views of the complainant. The complainant submitted that the representative had used her name and those of her two colleagues and implied that all three were in agreement with the project. Notwithstanding the use or not of the complainant's name the Panel considered that reference to discussions with the two consultants would positively influence the nurses and lead them to assume that the consultants favoured the programme. In the circumstances the Panel did not consider that it was adequate for the representative not to state that the consultants supported the programme; the representative should have stated unequivocally that the local consultants had not yet either approved or disapproved of the programme. Failure to explain the situation accurately would lead to the nurses drawing their own conclusions. The Panel considered that the representative had failed to maintain a high standard of ethical conduct and further breaches of Clauses 9.1 and 15.2 were ruled.

The Panel did not consider that the conduct of the representative warranted a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.

The Panel noted that it was unclear from the initial correspondence whether a complaint had been made about the Insulin for Life Programme *per se*. The complainant was more explicit when she had provided further comments on Aventis' response and had stated 'Whether the programme itself constituted a breach of the Code in terms of disguised promotion of Lantus was a decision for the Panel'. The complainant had referred, both in her initial letter and in her further comments, to practices only being eligible to take part in the programme if they agreed to prescribe Lantus for 10 patients. The Director thus decided that information had been received from which it appeared that Aventis might have contravened the Code; the complainant's comments about the Insulin for Life Programme would be taken up as a separate complaint (Case AUTH/1512/8/03).

Complaint received **19 June 2003**

Case completed **16 September 2003**

CASE AUTH/1483/6/03

PIERRE FABRE v AVENTIS PHARMA

Taxotere leavepiece

Pierre Fabre complained about a Taxotere (docetaxel) leavepiece, issued by Aventis Pharma, which informed readers that Taxotere was newly licensed for use, in combination with cisplatin, in chemo-naïve patients with advanced non-small cell lung cancer (NSCLC). Pierre Fabre supplied Navelbine (vinorelbine).

Page 3 of the leavepiece gave details of the design of the Tax 326 study which was a pivotal study in NSCLC. The description of the study design included the dose and schedule information for all three arms of the study including one in which Taxotere was given in combination with carboplatin. Taxotere was only licensed for use in combination with cisplatin. Pierre Fabre alleged that the description of the Taxotere/carboplatin arm amounted to promotion of an unlicensed indication.

The Panel did not accept Aventis' submission that it had to fully describe all three arms of the study in order to provide complete and accurate information. In the Panel's view it would have been sufficient to state that the study was a three arm study without giving details of the unlicensed Taxotere/carboplatin regimen. The Panel considered that the inclusion of such information constituted promotion of an unlicensed combination. A breach of the Code was ruled.

Upon appeal by Aventis the Appeal Board noted that the Taxotere summary of product characteristics (SPC) gave the dosage and schedule details of the Tax 326 study. The description of the study in the leavepiece was not inconsistent with the SPC; as in the SPC no reference to the outcome of treatment with Taxotere and carboplatin was given. The Appeal Board considered that in the context of a factual statement regarding the design of the Tax 326 study, the description of the treatment regimen of the Taxotere/ carboplatin arm of the study in the leavepiece did not constitute promotion of an unlicensed combination. No breach of the Code was ruled.

Pages 4 and 5 of the leavepiece featured three graphs comparing the outcome of treatment with either Taxotere/cisplatin or vinorelbine/cisplatin (two of the treatment arms in the Tax 326 study). Beneath the heading on page 4 it was explained that because Tax 326 was a 3 arm study, the level of significance required was p=0.025. Each graph showed an advantage for Taxotere/cisplatin: overall survival p=0.044; 2 year survival p=0.044 and response rate p=0.029. All of these p values were non-significant. Pierre Fabre alleged that the presentation of graphs with p values of < 0.05 was misleading as readers might assume the p values to imply significance. The explanation of the level of significance in a 3 arm study was insufficient and too remote to correct this misleading presentation.

The Panel accepted that pages 4 and 5 started with an explanation regarding the level of significance required although noted that this was in quite small print. All three graphs gave the visual impression of a clinically significant advantage for Taxotere/cisplatin. The presence of p values did not negate this impression; the explanation about the level of statistical significance was not sufficiently prominent. The impression of a meaningful clinical advantage for Taxotere/cisplatin was strengthened by the claims 'Taxotere and cisplatin: *Improving* patient outcomes …', '50% relative *improvement* in 2 year survival vs [vinorelbine/cisplatin]' (emphasis added). In reality there was no difference between the two regimens. The Panel considered that the material was misleading and a breach of the Code was ruled.

Pierre Fabre Ltd complained about an eight page leavepiece (ref TAX 860/04/03) for Taxotere (docetaxel) issued by Aventis Pharma Ltd. The front cover of the leavepiece featured highlighted boxes in which was stated 'New indication' and 'Taxotere (docetaxel) in combination with cisplatin in chemo-naïve patients with advanced non-small cell lung cancer [NSCLC]'.

Pierre Fabre supplied Navelbine (vinorelbine).

1 Promotion of an unlicensed combination

Page 3 was headed 'Tax 326 – A pivotal study in NSCLC' and gave details of a study designed to compare two 3-weekly cycle Taxotere combinations to vinorelbine/cisplatin in chemotherapy näive patients with stage IIIb or IV NSCLC.

COMPLAINT

Pierre Fabre stated that the description of the study design included the dose and schedule information for Taxotere with carboplatin, one of the three arms of the study. Taxotere was only licensed for use in combination with cisplatin. It was alleged that this was promotion of an unlicensed combination in breach of Clause 3.2 of the Code.

RESPONSE

Aventis stated that the Taxotere plus cisplatin combination, referred to on the front page of the leavepiece, was licensed in January 2003. Throughout the leavepiece, reference was only and clearly made to this licensed combination. There were no ambiguous references made to the use of Taxotere plus carboplatin, or indeed, the platinum class.

The full description of the study design was presented to provide complete and accurate information on the study. Without a reference to the Taxotere plus carboplatin arm, the description of the study would have been incomplete, inaccurate and misleading. In addition, a three-arm study meant that the level of significance was half that of the commonly accepted p value of < 0.05. This was referred to as the Bonferroni correction (Bland *et al* 1995). Therefore, without a description of the three-arm design, it would appear to be illogical to state the use of the Bonferroni correction, which was discussed on page 4 of the leavepiece.

The presentation of the full study design was analogous to the presentation of important dose ranging studies which referred to unlicensed doses.

Aventis therefore denied the allegation that it had promoted an unlicensed combination of Taxotere plus carboplatin in a way which was in breach of Clause 3.2 of the Code.

PANEL RULING

The Panel noted that the page included a description of the treatment schedules of the three arms of the study. The Panel did not accept Aventis' submission that it had to fully describe the three arms of the study in order to provide complete and accurate information. In the Panel's view it would have been sufficient in the circumstances to state that the study was a three arm study without giving full details of the unlicensed Taxotere plus carboplatin regimen. Clause 3.2 of the Code stated that promotion had to be in accordance with the marketing authorization and not inconsistent with the summary of product characteristics (SPC). The Panel considered that the inclusion of the information about Taxotere plus carboplatin in the leavepiece constituted promotion of an unlicensed combination. The Panel ruled a breach of Clause 3.2 of the Code.

APPEAL BY AVENTIS PHARMA

Aventis stated that the leavepiece was designed for use with an informed audience of oncologists and healthcare specialists associated with the treatment of cancer in the UK. Page 2 contained general epidemiological and treatment facts about lung cancer in the UK. The remaining five pages were all dedicated to the Tax 326 study which was used for the registration of the NSCLC indication of Taxotere in the European Union and had now been published in the Journal of Clinical Oncology (Fossella *et al* 2003).

The licensed indication for Taxotere in NSCLC, was set out in Section 4.1 of the SPC:

> 'TAXOTERE (docetaxel) is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.
>
> TAXOTERE in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition.
>
> The use of docetaxel should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy.'

Aventis submitted that from this it was clear that Taxotere was indicated for the treatment of NSCLC in combination with cisplatin, but not with carboplatin.

Aventis stated that nowhere in the leavepiece was it either stated or even suggested that Taxotere was indicated for use with carboplatin. On the bottom of page 7 there was a text box clearly stating the indicated dosing schedule and the SPC was referenced in superscript.

There was mention of the treatment of patients with a combination of Taxotere and carboplatin as a part of the description of the trial design of the Tax 326 study which was set out on page 3. This was the only place that the existence of this combination regimen was mentioned anywhere in the leavepiece.

Aventis submitted that it was scientifically correct when presenting trial data in summary form, such as in the leavepiece, to include an appropriate description of the test and control arms of the trial design. Aventis believed that it was not good scientific practice to choose only to present the arms, and / or sub-sets of a complex study, without mention of the other treatment considerations in the trial design. By only presenting two of the three arms of this study it was extremely likely that even an informed oncology specialist would be misled. This was particularly the case when the test arm significance levels were reported as p=0.044. With no mention of the third arm the reader could be excused for concluding that such a result should be assessed against the normal two-tail 0.05 test level. This would be wrong. Stating that a significance value of 0.025 should be used instead would require detailed explanation and the only way of doing this would be to refer to the presence of a third arm in the study. Aventis submitted that it had been scientifically correct in presenting the data this way.

Aventis submitted that the leavepiece was consistent with the SPC; Section 5.1 contained a sub-section titled 'Taxotere in combination with platinum agents in chemotherapy-naïve patients'. The first paragraph of this sub-section described the design of the pivotal study and made specific note of all three arms, control and in combination with cisplatin and carboplatin. The presentation of the survival table below this paragraph only referred to data relating to the licensed cisplatin combination. Aventis submitted that it had presented this data in accordance with the terms of its marketing authorization and that was not inconsistent with the particulars of the SPC. To present it in any other way than that which Aventis had done would, in its view, be a breach of Clause 3.2.

Section 5.1 of the Taxotere SPC stated:

> 'In a Phase III trial, 1218 patients with unresectable stage IIIB or IV NSCLC, with KPS [Karnofsky Performance Status Scale] of 70% or greater, and who did not receive previous chemotherapy for this condition, were randomised to either Taxotere (T) 75mg / m^2 as a 1 hour infusion immediately followed by cisplatin (Cis) 75mg / m^2 over 30-60 minutes every 3 weeks, Taxotere 75mg / m^2 as a 1 hour infusion in combination with carboplatin (AUC 6mg / ml / min) over 30-60 minutes every 3 weeks, or vinorelbine (V) 25mg / m^2 administered over 6-10 minutes on days 1, 8, 15, 22 followed by cisplatin 100mg / m^2 administered on day 1 of cycles repeated every 4 weeks.
>
> Survival data, median time to progression and response rates for two arms of the study are illustrated in the following table ...'.

Aventis noted that Fossella *et al* reported 1,220 patients, whilst the SPC reported 1,218 patients. The reason for this was that two patients were randomised in the study but were not treated because they had not had lung cancer. Fossella *et al* reported on an intention

to treat basis and the SPC reported only patients with lung cancer – ie reported on a licensed for use basis.

COMMENTS FROM PIERRE FABRE

Pierre Fabre stated that it considered this to be a clear and straightforward breach of the Code and had nothing further to add.

APPEAL BOARD RULING

The Appeal Board noted Section 5.1 of the Taxotere SPC in relation to NSCLC. The Appeal Board considered that the description of the third arm of the Tax 326 study in the leavepiece as '75mg/m^2 Taxotere plus AUC 6mg/ml/min carboplatin q3 weeks (n=406)' was not inconsistent with the Taxotere SPC. The Appeal Board noted that, as in the SPC, the leavepiece contained no reference to the outcome of treatment with Taxotere in combination with carboplatin. Thus the Appeal Board considered that in the context in which it appeared, ie a factual statement regarding the design of the Tax 326 study, the inclusion of the description of the treatment regimen of the Taxotere/carboplatin arm of the study in the leavepiece at issue did not constitute promotion of an unlicensed combination. The Appeal Board ruled no breach of Clause 3.2 of the Code. The appeal on this point was successful.

2 Misleading statistical information

Page 4 was headed 'Taxotere and cisplatin: Improving patient outcomes in advanced NSCLC'.

Pages 4 and 5 included three graphs comparing Taxotere and cisplatin with vinorelbine and cisplatin with regard to overall survival, 2 year survival and response rate. Beneath the heading on page 4 an explanation appeared 'N.B. Boneferroni (sic) correction method: Given that Tax 326 was a 3 arm study, the level of statistical significance required was p=0.025'.

Each graph showed an advantage for Taxotere and cisplatin. The p values were overall survival p=0.044, 2 year survival p=0.044 and response rate p=0.029. All of these p values were non-significant.

COMPLAINT

Pierre Fabre stated that the statistical methods employed in this three-arm study required a p value < 0.025 for significance. There were no statistically significant differences between Taxotere and cisplatin and Navelbine and cisplatin, in terms of overall survival, 2 year survival or response rates in this study as clearly stated in the US Taxotere prescribing information.

The visual presentation of only two arms of the study suggested that a p-value of <0.05 would be required as this was the commonly accepted p value for a two-arm study. The presentation of the p-value in the three graphs (<0.05) was misleading in that the reader might interpret the p values given on the three graphs to imply significance. The position of the supplementary 'N.B.' statement in small italic type near the top of page 4 was insufficient and too remote to correct this misleading presentation.

The leavepiece suggested a significant result that was contrary to the actual result of the clinical trial. This was misleading and was alleged to be in breach of Clause 7.2 of the Code.

RESPONSE

Aventis was aware of the potential confusion over the p value for the 3-arm study. Hence the Bonferroni correction and the effect on the level of significance were clearly stated at the top of the page, underneath the heading on page 4. This was positioned before the discussion of any data, rather than as a footnote, for greater clarity.

Further, each of the three graphs had a comment underneath. Statistical significance had not been stated or implied at any point on these pages: Overall survival graph – it was clearly stated that the survival curves showed a 'trend' rather than a statistically significant improvement. Two year survival graph – '50% relative improvement in 2 year survival'. This had not stated a statistically significant improvement. Response rate graph – '28% increased response rate'. This had not stated a statistically significant difference.

The only area where a statistically significant difference was referred to was in the quality of life indices on pages 6 and 7, not on pages 4 and 5, to which the alleged breach referred to. The summary on page 7 stated a trend for improvement in overall survival and this further negated the allegation that the information was misleading.

Aventis therefore denied the allegation that statistical information was presented in a way which was in breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the results of the study were presented on a double page spread beneath the heading 'Taxotere and cisplatin: Improving patient outcomes in advanced NSCLC'.

The Panel accepted that the pages started with an explanation that the level of statistical significance required was p=0.025 although noted that this was in quite small print. All three graphs gave the visual impression that there was a clinically significant difference between the products in favour of Taxotere and cisplatin. The presence of p values did not negate this impression; the explanation about the level of statistical significance was not sufficiently prominent.

The impression of a meaningful clinical advantage for Taxotere/cisplatin was strengthened by the claims 'Taxotere and cisplatin: *Improving* patient outcomes in advanced NSCLC', '50% relative *improvement* in 2 year survival vs [vinorelbine/cisplatin]' and '28% *increased* response rate vs [vinorelbine/cisplatin]' (emphasis added). In reality the study cited (Fossella *et al* 2001) had shown no difference between the products in terms of overall survival, 2 year survival or response rate. The Panel considered that the material was misleading and a breach of Clause 7.2 of the Code was ruled.

Complaint received **24 June 2003**

Case completed **8 October 2003**

PRIMARY CARE TRUST MEDICAL DIRECTOR v MERCK SHARP & DOHME and SCHERING-PLOUGH

Sampling of Ezetrol

The medical director of a primary care trust (PCT) complained that Merck Sharp & Dohme and Schering-Plough were offering GPs up to six months' supply of Ezetrol (ezitimibe) free of charge on the basis of 'familiarization and demonstration of efficacy'. The complainant noted that Ezetrol was an oral medicine. There was nothing novel in its presentation or route of administration that warranted an extended period of familiarization and 'dealing' with Ezetrol would involve the same procedures as already followed for statins.

The Panel noted that Merck Sharp & Dohme and Schering-Plough had started a programme for physicians to provide practice support and an opportunity to assess the response of patients to Ezetrol. The arrangements were for six patients per programme and one programme per doctor. Doctors were supplied with six sample packs which were intended to provide an opportunity to assess the efficacy of Ezetrol in six patients over one month. The Panel considered that the packs of Ezetrol were supplied as samples; they had been provided to GPs and it appeared that only six samples had been given. No breach of the Code was ruled.

The medical director of a primary care trust (PCT) complained about the provision of Ezetrol (ezitimibe) by Merck Sharp & Dohme Limited and Schering-Plough Ltd.

Ezetrol was a cholesterol absorption inhibitor indicated to be co-administered with a statin as an adjunctive therapy to diet for use in patients with certain types of hypercholesterolaemia who were not appropriately controlled by a statin alone. Ezetrol was promoted by Merck Sharp & Dohme and Schering-Plough.

COMPLAINT

The complainant stated that Merck Sharp & Dohme and Schering-Plough representatives were offering GPs up to six months' supply of Ezetrol free of charge on the basis of 'familiarisation and demonstration of efficacy'; the companies considered that this offer fell within the guidance in the Code on the distribution of samples to the medical profession.

Clause 17 of the Code defined a sample as:

> 'a small supply of medicine provided to health professionals so that they may familiarise themselves with it and acquire experience in dealing with it.'

The complainant stated that Ezetrol was an oral medicine. There was nothing novel in its presentation or route of administration that warranted an extended period of familiarisation. In 14 years of general practice, no pharmaceutical representative had ever offered the complainant free supplies of medicine, beyond starter packs for emergency use. There was no indication for the emergency administration of lipid-lowering medicine in primary care.

The complainant assumed that 'dealing with' Ezetrol would involve measurement of blood lipids and monitoring the patient for any potential adverse reactions; in other words, exactly the same procedure any GP would follow when prescribing a statin, for example. None of the statin manufacturers had offered free supplies of their medicines to GPs.

Clause 17 of the Code also stated that:

> 'Titration packs, free goods and bonus stock… are not samples'.

The complainant defined this offer as being an offer of 'free goods'.

The complainant stated that a local prescribing committee had produced guidance on the role of Ezetrol. It acknowledged that there were circumstances in which its use might be appropriate, such as those patients in whom a statin might be contra-indicated or in those taking the maximum tolerated dose of such medicines. The key word here was 'maximum'. Statins had a flat pricing structure for all but their minimum doses. The introduction of a second medicine in a patient who was on a less than maximal dose of a statin, and who showed no adverse effects did not represent cost-effective prescribing. The companies did not, in either their promotional literature or representative presentations, make any mention of the need to titrate the dose of statin to its maximum tolerated level before considering Ezetrol. There was, therefore, no reason to believe they would change the information accompanying the proposed free medicine.

Growth in statin prescribing was inevitable, and likely to increase following the acceptance by GPs of their new contract. The cost of lipid-lowering medicines was one of the prime causes of PCT prescribing overspends throughout England. The marketing tactics employed by Merck Sharp & Dohme and Schering-Plough were at variance with PCTs' duty to obtain best value for public money.

The complainant alleged that the marketing strategy for Ezetrol was in breach of Clause 17 of the Code. In particular, there was no valid clinical reason for supplying the medicine free to GPs.

When writing to Merck Sharp & Dohme and Schering-Plough to advise them of the complaint the Authority invited them to respond in relation to Clauses 2, 9.1, 15.2 and 18.1 of the Code in addition to Clause 17 which had been referred to by the complainant.

RESPONSE

Merck Sharp & Dohme and Schering-Plough responded separately but in similar terms.

The companies noted the complainant's allegation that their representatives were offering general practitioners up to six months' supply of Ezetrol free of charge on the basis of 'familiarisation and demonstration of efficacy'. The companies confirmed that they did not supply medicine free to general practitioners but, in common with many pharmaceutical companies, they did supply samples from time to time.

In the case of Ezetrol, the companies had not authorised their representatives to supply free medicine, which they accepted would be in breach of the Code, but it was currently possible to supply samples of Ezetrol in accordance with the guidelines detailed below.

Ezetrol was a new medicine that was first in its class as a specific cholesterol absorption inhibitor. To facilitate familiarity with this new class Merck Sharp & Dohme and Schering-Plough might make sample packs available to health professionals.

To comply with Clause 17 of the Code, the representatives promoting Ezetrol had been reminded that:

- Samples must only be given to health professionals qualified to prescribe such a product.
- Up to six samples might be given to any one general practitioner during 2003 so that up to six suitable patients might be treated (and a patient record card was also available to GPs should they wish to record their experiences in using Ezetrol). Clause 17.2 specified up to ten sample packs during the course of a year.
- Samples could only be provided in response to written requests which had been signed and dated.
- A sample of medicine must be no larger than the smallest presentation of the medicine on the market; for Ezetrol this was a 28-day calendar pack.
- Each sample must be marked 'free medical sample – not for resale' and must be accompanied by a summary of product characteristics for Ezetrol.
- Samples distributed by representatives must be handed direct to the health professional requesting them or persons authorised to receive them on their behalf.

These instructions were issued verbally in representative briefing meetings and also in a briefing document (GP Experience Programme briefing document).

The companies agreed that there was no indication for the emergency administration of oral lipid-lowering therapy in primary care and the samples were not provided on that basis. As a significant clinical effect of Ezetrol was seen within two weeks (Gagné *et al* 2002), a 28-day sample of the medicine gave a health professional a fair trial for familiarisation and experience of Ezetrol.

The companies noted that the complainant had stated that representatives were offering GPs up to six months' supply free of charge, and wondered whether a misunderstanding had arisen given the fact that they might offer a health professional, on written request, up to six 28-day packs of Ezetrol; these would be for a twenty-eight day trial for up to six individual patients chosen by the health professional.

The practice to which the companies assumed the complainant was referring did not involve the provision of free goods, titration packs, or bonus stock, but the managed provision of sample packs in accordance with Clause 17.

PANEL RULING

The Panel noted that Merck Sharp & Dohme and Schering-Plough had started a programme for physicians to provide practice support and an opportunity to assess the response of patients to Ezetrol. A document for representatives 'Dual Inhibition Utility through Audit of Lipids' was provided. This set out the arrangements for the programme which was for six patients per programme and one programme per GP. The document reminded representatives of the requirements of Clause 17 of the Code and specifically stated that six samples could be given provided the GP signed for them. The instructions stated that representatives were to ensure that each doctor only received these six samples.

The Code permitted companies to provide samples of a medicine to health professionals qualified to prescribe that product in order that they might familiarise themselves with it and acquire experience in dealing with it. No more than ten samples of a particular medicine might be provided to an individual health professional during the course of a year. The relevant requirements regarding pack size and labelling etc had to be met.

The Panel noted that Merck Sharp & Dohme and Schering-Plough were providing doctors with six sample packs. Each sample was a 28-day pack which was the smallest presentation on the market. The six samples were intended to provide an opportunity to assess the efficacy of Ezetrol in six patients over one month.

The Panel considered that the packs of Ezetrol were supplied as samples; they were neither free goods nor starter packs as defined in the Code. The supply of Ezetrol had to comply with the sample requirements in the Code. There was no allegation that a signature had not been obtained nor that the packs had not been appropriately labelled and thus the Panel made no rulings in this regard. They had been provided to GPs and it appeared that only six samples had been provided. The Panel thus ruled no breach of Clauses 17.1, 17.2 and 17.4 of the Code.

Given its rulings of no breach above the Panel also ruled no breach of Clauses 2, 9.1, 15.2 and 18.1 of the Code.

Complaint received **25 June 2003**

Case completed **5 August 2003**

ANONYMOUS
v SOLVAY HEALTHCARE and ABBOTT LABORATORIES

Conduct of representatives

An anonymous complaint was received about the conduct of two representatives, one from Solvay Healthcare the other from Abbott Laboratories. The complainant stated that the representatives were detailing each other's products which confused the GPs.

The Panel noted the companies' submissions that the allegation was false. No breach of the Code was ruled.

An anonymous complaint was received about the conduct of two medical representatives, one from Solvay Healthcare Limited and the other from Abbott Laboratories Limited. It was established practice that anonymous complaints were to be accepted and dealt with in the usual way.

COMPLAINT

The complainant stated that the two representatives were detailing each other's products which confused the GPs. The complainant stated that the representatives' managers were aware of what the representatives were doing but as sales were good they allowed the practice to continue.

The Authority asked Solvay Healthcare and Abbott Laboratories to respond in relation to the requirements of Clauses 9.1 and 15.2 of the Code.

RESPONSE

Solvay Healthcare and Abbott Laboratories submitted separate but identical responses.

Solvay Healthcare and Abbott Laboratories stated that neither representative had ever undertaken detailing of the other's products. The companies thus denied breaches of Clauses 9.1 and 15.2 of the Code.

The companies noted that it was accepted industry practice for representatives from different companies to share facilities and desk space at promotional events and it might have been this practice which caused confusion resulting in this complaint.

The companies confirmed that they did not co-promote any product in the UK.

PANEL RULING

The Panel noted Solvay Healthcare and Abbott Laboratories' submissions that the two representatives had not detailed each other's products as alleged. The Panel thus accordingly ruled no breach of Clauses 9.1 and 15.2.

Complaint received **16 July 2003**

Case completed **30 July 2003**

PHARMACEUTICAL COMPANY EMPLOYEE v GLAXOSMITHKLINE

Requip journal advertisement

An employee of KuDOS, a pharmaceutical research company, complained in a private capacity about a journal advertisement for Requip (ropinirole) issued by GlaxoSmithKline. Requip was licensed for the treatment of idiopathic Parkinson's disease.

The top left hand corner of the advertisement read 'Imagine if you were in a queue. And you suddenly couldn't move. And, instead of help you got abuse' and appeared above a photograph taken from the viewpoint of a person in a queue at whom others were staring. A man was leaning towards the unseen object of attention stating 'You in this bleedin' queue or not?' A strapline read 'Fights Parkinson's. Defends dignity'.

The complainant alleged that the advertisement was in bad taste. The look of the man said it all, so why did GlaxoSmithKline feel the need to add offensive text? Such advertisements simply offended. Whatever happened to those canons of good taste?

The Panel noted that the Code required all material and activities to recognise the special nature of medicines and the professional nature of the audience to whom they were directed and not be likely to cause offence.

ReQuip was indicated for the treatment of idiopathic Parkinson's disease and the Panel noted the company's submission that the scene depicted was not unfamiliar to patients with the disease in which rigidity, on-off phenomena and difficulty in initiating movement could cause embarrassment. The Panel thus considered that the complainant's view of the advertisement would not be shared by the majority of the audience. The Panel considered that the advertisement was not unreasonable in relation to the requirements of the Code and no breach was ruled.

An employee of KuDOS Pharmaceuticals, a pharmaceutical research company, complained in a private capacity about a journal advertisement (ref REQ/FPA/03/5435) for ReQuip (ropinirole) issued by GlaxoSmithKline UK Ltd which had appeared in the BMJ, 5 July 2003. Requip was licensed for the treatment of idiopathic Parkinson's disease.

Text in the top left hand corner of the advertisement read 'Imagine if you were in a queue. And you suddenly couldn't move. And, instead of help you got abuse' and appeared above a photograph taken from the viewpoint of a person at the back of a queue at whom people both in the queue and being served at a counter were staring. A man was leaning towards the unseen object of attention stating 'You in this bleedin' queue or not?' A strapline read 'Fights Parkinson's. Defends dignity'.

It had previously been decided, following consideration by the then Code of Practice Committee and the ABPI Board of Management, that private complaints from pharmaceutical company employees had to be accepted. To avoid this becoming a means of circumventing the normal procedures for intercompany compaints, the employing company would be named in the report. The complainant would be advised that this would happen and be given an opportunity to withdraw the complaint. The present complaint had not been so withdrawn.

COMPLAINT

The complainant alleged that the advertisement was in bad taste. The look of the enquiring person said it all, so why did GlaxoSmithKline feel the need to add offensive text? The complainant stated that he was not a prude and was sure that in the right place and at the right time he could mix vernacular with the best of them. However he preferred not to see the medical press joining the gutter press, even if this was to be GlaxoSmithKline's intention. Such advertisements simply offended. Whatever happened to those canons of good taste?

When writing to GlaxoSmithKline the Authority asked it to respond in relation to Clause 9.2 of the 2003 edition of the Code.

RESPONSE

GlaxoSmithKline regretted that the complainant considered the advertisement offensive; it was not intended to be so or to lower the high standards of the medical press.

However, GlaxoSmithKline strongly believed that the advertisement did not contravene Clause 9.2 of the Code. The scene depicted was one not unfamiliar to patients with Parkinson's disease, in which rigidity, on-off phenomena and difficulty in initiating movement could cause embarrassment in a public place and lead to lack of understanding by others. This situation was clearly described by the most prominent text at the top of the advertisement, 'Imagine if you were in a queue. And you suddenly couldn't move. And, instead of help you got abuse'. The artwork was intended to depict this and provided a specific example of just such an occasion. The words spoken were carefully selected in order to strike a balance between creating the desired impact, supporting the body language of the man depicted and reflecting a real-life scenario, whilst avoiding the use of swear-words. Indeed, the Collins Concise Dictionary defined 'bleedin' as being a slang term used as a sentence intensifier, yet not as an offensive or taboo term.

Whilst GlaxoSmithKline regretted that the complainant claimed to have been offended by the advertisement, it had been published widely in the medical press since February 2003, including in the

'BMJ', 'Hospital Doctor', 'Health & Ageing', 'Progress in Neurology', 'Neurology and Advances in Clinical Neuroscience' and 'Rehabilitation'. Despite this wide coverage, GlaxoSmithKline had not received any other complaints or negative comments about this material, which suggested that the likelihood of this advertisement to cause offence was minimal.

PANEL RULING

The Panel noted that Clause 9.2 of the 2003 edition of the Code required that all material and activities must recognise the special nature of medicines and the professional nature of the audience to which they were directed and must not be likely to cause offence.

The Panel noted that ReQuip was indicated for the treatment of idiopathic Parkinson's disease. The Panel also noted the company's submission that the scene depicted was not unfamiliar to patients with the disease in which rigidity, on-off phenomena and difficulty in initiating movement could cause embarrassment in a public place.

The Panel noted that the complainant had found the text in the advertisement offensive. Given the therapeutic area and scene depicted in the advertisement the Panel considered that this view would not be shared by the majority of the audience. The Panel considered that the advertisement was not unreasonable in relation to the requirements of Clause 9.2 and no breach of that clause was ruled.

Complaint received **22 July 2003**

Case completed **16 September 2003**

CASE AUTH/1499/7/03

LAGAP v PROCTER & GAMBLE

Promotion of Asacol

Lagap complained about a 'Dear Doctor' letter, a 'Dear Pharmacist' letter and a journal advertisement promoting Asacol (mesalazine) and issued by Procter & Gamble. Lagap supplied Ipocol (also mesalazine).

The 'Dear Doctor' letter featured a table which listed, *inter alia,* delayed release mesalazine preparations and their release characteristics in which Asacol was described as having 'Eudragit S coating dissolving at pH>7'. Lagap's product, Ipocol, was described as having a 'Polymer resin coating'. Ipocol and Asacol were both coated with Eudragit S, which dissolved at pH>7. Lagap alleged that the table was misleading as a distinction had been made between the coating on Ipocol and Asacol where none existed.

The Panel noted that the tablet coating and release characteristics of Asacol had been stated in detail. The only comparable information given for Ipocol was that it had a 'Polymer resin coating'. The Ipocol summary of product characteristics (SPC) stated that the tablets were designed to disintegrate above pH 7 to release the active drug and methacrylic acid polymer was listed as one of the excipients.

The Panel noted that the description 'Polymer resin coating' was based on the Ipocol SPC dated June 1998 and provided to Procter & Gamble by Lagap in August 2002. The Panel noted Procter & Gamble's submission that the description given in the Ipocol SPC could apply to any Eudragit polymer coating as well as certain coatings from other suppliers. The Panel considered that at 28 October 2002, when the 'Dear Doctor' letter was sent, Procter & Gamble did not know whether methacrylic acid copolymer referred to Eudragit S or a coating from another supplier and thus the description 'Polymer resin coating' was a fair reflection of the information provided by Lagap and was not misleading in this regard. No breach of the Code was ruled.

In the Panel's view, however, the disintegration characteristics of the tablets should have been included in the table as they were for other tablets. It was misleading not to have noted that the polymer resin coating was designed to disintegrate above pH 7. Failure to include such information implied a difference in that regard between Asacol and Ipocol when there was none. A breach of the Code was ruled.

The 'Dear Pharmacist' letter, headed 'Switching of mesalazine 400mg preparations' stated, *inter alia,* 'Although Asacol and Ipocol are both mesalazine 400mg modified release tablets, they have significantly different *in vitro* release characteristics. This may have implications for the common practice of targeting release of mesalazine based on the site and extent of a patient's disease'. This statement was referenced to Podolsky (2002).

Lagap stated that despite there being no data to support the extrapolation of the *in vitro* data for Ipocol and Asacol to the clinical situation, Procter & Gamble had used such data prominently and without adequate qualification as to its significance, to extrapolate to the clinical situation. This was alleged to be misleading. Procter & Gamble had failed to provide any data to show that the *in vitro* data was of direct relevance and significance to the clinical situation.

The Panel noted that the letter was headed 'Switching of mesalazine 400mg preparations' and discussed the reason as to why it was important to ensure that patients already on Asacol continued to receive that brand and were not inadvertently switched to Ipocol. The different *in vitro* release characteristics of Asacol and Ipocol were discussed and that this 'may have implications for the common practice of targeting release of mesalazine based on the site and extent of a patient's disease'.

Appended to the letter was a page headed '*In vitro* dissolution testing of Asacol and Ipocol tablets' which discussed the products' *in vitro* dissolution profiles in pH 7.2 and pH 6.4. The final paragraph read '… the dissolution profile of a mesalazine formulation mediates the site of release and hence the ultimate colonic concentration. The colonic mucosal concentration of mesalazine has been correlated with clinical effect. … Asacol and Ipocol have different release characteristics at both pH 6.4 and pH 7.2'.

The Panel noted that the British National Formulary, March 2003, stated that the 'delivery characteristics of enteric coated mesalazine preparations may vary; these preparations should not be considered interchangeable'.

On balance the Panel considered that the letter explained the difference in release characteristics between Asacol and Ipocol and why this difference was important. No clinical advantage was claimed. No breach of the Code was ruled.

An advertisement headed 'Management of Ulcerative Colitis The Role of the Pharmacist' included a graph comparing the dissolution results of Asacol and Ipocol, expressed as a % of available mesalazine after 1 hour in pH 7.2 buffer. Ipocol released a statistically significant greater percentage of available mesalazine than Asacol at 10, 20 and 30 minutes; p< 0.0001. The graph was derived from data on file. The article stated that the graph showed that the rate of release of Ipocol was markedly different from Asacol.

Lagap alleged that the graph did not give a clear, fair or balanced view of the matters with which it dealt and misled by its incompleteness. The study in question had three stages; only the last stage, where the differences between Ipocol and Asacol were more noticeable, was published. The graph implied that an Ipocol tablet only delivered around 70% of the available mesalazine whilst an Asacol tablet delivered close to 100%. This was misleading since Ipocol tablets also delivered 100% of the available mesalazine during the study.

The Panel noted that the study had three stages, each mimicking exposure to the pH of the stomach, proximal small bowel and terminal small bowel/proximal colon respectively. Data for the third stage, which mimicked the conditions of that part of the gastrointestinal tract in which Ipocol and Asacol were designed to release mesalazine, was depicted on the graph at issue. A footnote to the graph read 'Ipocol – at this stage 73% of available mesalazine released following 27% released at pH 6.4. Asacol – at this stage 100% mesalazine released following < 1% at pH 6.4'.

The Panel noted that the advertisement discussed the data on file and the three stage study methodology beneath the heading '*In vitro* dissolution testing'. The products' respective release profiles over the three stages were discussed.

The Panel noted that the graph was clearly labelled 'Dissolution results … after 1 hour in pH 7.2 buffer'; pH 7.2 reflecting the conditions found in the colon and terminal ileum. The Panel considered that within the overall context of the advertisement the graph was not misleading about the products' respective release profiles; sufficient information had been provided about the study methodology. No breach of the Code was ruled.

Lagap stated that the graph was inaccurate and misleading in that it showed a greater difference between Ipocol and Asacol than the data on file on which it was based.

The Panel noted that on the graph depicted in the data on file the difference in percentage release of available mesalazine between Asacol and Ipocol at 10 minutes was approximately 18%, whilst on the graph in the advertisement it was approximately 52%. The Panel considered the graph misleading in this regard, as acknowledged by Procter & Gamble. A breach of the Code was ruled.

Lagap Pharmaceuticals Ltd complained about the promotion of Asacol (mesalazine) by Procter & Gamble Pharmaceuticals UK, Limited. Three promotional items were at issue; a 'Dear Doctor' letter, a 'Dear Pharmacist' letter and a journal advertisement.

Lagap produced a mesalazine product, Ipocol. Lagap explained that ulcerative colitis was a chronic inflammatory disease affecting the mucosa of the large bowel and occasionally the distal ileum. Mesalazine (5-aminosalicyic acid (5-ASA)) was a standard therapy for ulcerative colitis, exerting its anti-inflammatory effects topically on the affected mucosa. Since immediate release formulations provided rapid and almost complete absorption of mesalazine, a variety of pro-drug and modified release formulations had been developed to target release of mesalazine more effectively.

Ipocol and Asacol both contained 400mg of mesalazine in a tablet coated with Eudragit S (methacrylic acid copolymer), a pH sensitive resin that was soluble in intestinal fluid from pH 7. This was designed to protect mesalazine in the more acidic conditions found higher in the small intestine whilst allowing release towards the end of the ileum. Since mesalazine exerted its effects topically on the gut mucosa there was no direct correlation between its bioavailability and clinical effect.

Ipocol was launched in the UK in August 2002, although the product had been available in Europe for over 12 years.

A 'Dear Doctor' letter dated 28 October 2002 (ref A5 1834)

The letter, headed 'Unintended switching of mesalazine 400mg preparations', stated that previously patients had received Asacol 400mg tablets when mesalazine 400mg was prescribed and advised that Ipocol, a proprietary-named mesalazine 400mg product had just been launched in the UK. The final paragraph referred to an attached summary of the available oral aminosalicyates. Page 2 provided background information on oral aminosalicylates and featured a table which listed *inter alia* delayed release mesalazine preparations and release characteristics.

COMPLAINT

Lagap noted that whilst Asacol and Salofalk were respectively described as having 'Eudragit S coating dissolving at pH>7' and 'Eudragit L coating dissolving at pH>6', Ipocol was described as having a 'Polymer resin coating'. Ipocol and Asacol were both coated with Eudragit S, which dissolved at pH>7. A distinction had therefore been made between the coating agent used by Ipocol and Asacol where none existed. This was alleged to be misleading in breach of Clause 7.2 of the Code. Lagap noted that Procter & Gamble's defence was that the Ipocol summary of product characteristics (SPC) referred to 'methacrylic acid copolymer' and the company was therefore reflecting currently available information.

Lagap stated that according to the relevant European Guidelines 'methacrylic acid copolymer' was the appropriate name to be used for Eudragit S. There had been no change to Ipocol's SPC or patient information leaflet (PIL) in this respect since launch, as this had been the correct terminology to use over this period. Lagap also referred to the PIL for Asacol (prepared in October 2002) which stated that 'They [Asacol tablets] are covered with a coating called 'Eudragit S' (also known as methacrylic acid copolymer)'. This statement was not a recent addition to the Asacol PIL. The SmithKline Beecham version of the leaflet found on the Electronic Medicines Compendium (eMC) on 16 January 2003, with a preparation date of August 1999, contained exactly the same words.

In addition, Section 5.2 Pharmacokinetic properties of the Ipocol SPC stated 'Mesalazine enteric-coated tablets are designed to disintegrate above pH 7 to release the active drug'.

Hence Procter & Gamble had all the necessary information to confirm that Ipocol was coated with 'Eudragit S dissolving at pH>7' but chose to imply that it was different.

RESPONSE

Procter & Gamble stated that the description used in the 'Dear Doctor' letter was based on the Ipocol SPC supplied by Lagap. The SPC described the coating as 'methacrylic acid copolymer', and did not mention Eudragit S. The descriptor given in the SPC could apply to any Eudragit polymer coating, as well as to certain coatings from other suppliers. Further, Procter & Gamble understood that the pH of release did not specifically identify the coating that had been used, since release might be affected by factors such as coating thickness, or the combination of multiple coating types. This meant that, contrary to Lagap's assertion, Procter & Gamble could not have deduced with any certainty that Ipocol was coated with Eudragit S. The company therefore chose to use a broader description that would encompass all possibilities. This descriptor had not been used since Lagap advised in intercompany correspondence that the coating was in fact Eudragit S. Procter & Gamble had agreed in writing to use the specific term 'Eudragit S' for the description of the Ipocol tablet coating in future materials.

Procter & Gamble did not accept that this constituted a breach of Clause 7.2, as it neither misled the reader as to the nature of the coating, nor was it inaccurate.

PANEL RULING

The Panel noted that in the table at issue the tablet coatings and release characteristics of Asacol and Salofalk had been stated in detail. The only comparable information given for Ipocol was that it had a 'Polymer resin coating'. Section 5.2 of the Ipocol SPC, Pharmacokinetic properties, stated that mesalazine enteric-coated tablets were designed to disintegrate above pH 7 to release the active drug and Section 6, Pharmaceutical particulars, listed methacrylic acid polymer as one of the excipients.

The Panel noted that the description 'Polymer resin coating' was based on the Ipocol SPC dated June 1998 and provided to Procter & Gamble by Lagap on 19 August 2002. The Panel noted Procter & Gamble's submission that the description given in the Ipocol SPC could apply to any Eudragit polymer coating as well as certain coatings from other suppliers. The Panel considered that at 28 October 2002, when the 'Dear Doctor' letter was sent, Procter & Gamble did not know whether methacrylic acid copolymer referred to Eudragit S or a coating from another supplier and thus the description 'Polymer resin coating' was a fair reflection of the information provided by Lagap and was not misleading in this regard. No breach of Clause 7.2 was ruled. The Panel noted that Procter & Gamble had not used the description since being advised on 10 December 2002 that the coating was Eudragit S.

In the Panel's view, however, the disintegration characteristics of the tablets should have been included in the table as they were for the other tablets. The Panel considered that it was misleading not to have noted that the polymer resin coating was designed to disintegrate above pH 7. Failure to include such information implied a difference in that regard between Asacol and Ipocol when there was none. A breach of Clause 7.2 was ruled.

B 'Dear Pharmacist' letter dated 28 October 2002 (ref AS1834)

The 'Dear Pharmacist' letter, headed 'Switching of mesalazine 400mg preparations' stated, *inter alia*, 'Although Asacol and Ipocol are both mesalazine 400mg modified release tablets, they have significantly different *in vitro* release characteristics. This may have implications for the common practice of targeting release of mesalazine based on the site and extent of a patient's disease'. This statement was referenced to Podolsky (2002).

COMPLAINT

Lagap referred to the supplementary information to Clause 7.2 of the Code that 'Care must be taken with the use of such data [*in vitro*] so as not to mislead as to its significance. The extrapolation of such data to the clinical situation should only be made where there is data to show that it is of direct relevance and significance'.

Despite there being no data to support the extrapolation of the *in vitro* data for Ipocol and Asacol to the clinical situation, Procter & Gamble had used this *in vitro* data prominently and without adequate qualification as to its significance, to extrapolate to the clinical situation. Lagap therefore alleged that this was misleading.

Procter & Gamble had failed to provide any data (either in the cited reference in the 'Dear Pharmacist' letter or in its written response to Lagap's allegations on this point) to show that the *in vitro* data used in this 'Dear Pharmacist' letter (and a number of other advertisements) was of direct relevance and significance to the clinical situation.

In fact, the references provided did not appear to adequately support either the specific statements against which they were cited, in relation to their relevance to a comparison between Ipocol and Asacol, nor the wider issue of providing data to support the direct relevance of *in vitro* data to the clinical situation for such modified release mesalazine products.

Podolsky stated 'In general, a 5-aminosalicylate-based agent should be selected principally on the basis of disease location'. However, the author then described the most appropriate use of 5-ASA formulations based on broad formulation characteristics, grouping together: rectal formulations, compounds conjugated to prevent absorption by the small bowel including sulfasalazine, olsalazine and balsalazide and oral formulations in which 5-ASA was in a slow release or pH dependent matrix.

Both Ipocol and Asacol fell within the latter description of pH dependent matrices. The author commented that such formulations '… can deliver therapeutic concentrations to the more proximal small bowel or distal ileum …'. In other words, the author made no distinction between the use of such pH dependent and slow release products in terms of their delivery characteristics in man.

Given that differences in *in vitro* characteristics had been reported for such mesalazine products, particularly between slow release and pH dependent products this reference would appear to contradict the statement it was being used to substantiate.

In intercompany correspondence Procter & Gamble did not address the question; instead it responded by stating 'The **theoretical** link between *in vitro* and clinical data is widely accepted'.

Although Lagap accepted that a correlation might exist between *in vitro* and *in vivo* data for some products, this had not been shown for mesalazine modified release products. The Code required there to be data to show that the *in vitro* data was of direct relevance and significance to the clinical situation. The above statement and the references cited against it did not address these requirements.

RESPONSE

Procter & Gamble stated that when tested using the standard methodology for Asacol (as found in the UK Marketing Authorization application and in compliance with PhEur guidelines), there were statistically significant differences between the *in vitro* dissolution characteristics of Asacol and Ipocol tablets.

In the 'Dear Pharmacist' letter, care had been taken with the use of these *in vitro* data so as not to mislead as to their significance. It was clearly stated that these data were from *in vitro* experiments, and it was not claimed that they represented a clinical difference; no evaluation of relative efficacy was made. The letter informed the pharmacist of differences in the dissolution profiles of the two products, and stated 'This may have implications for the common practice of targeting release of mesalazine based on the site and extent of a patient's disease'.

This did not therefore constitute extrapolation of *in vitro* data to the clinical outcome, as prohibited by the Code, but rather described how the data might be of relevance to the health professional when making a prescribing decision (regarding whether to allow the products to be viewed as interchangeable for the individual patient). The reader was therefore at liberty to decide the significance given to these data. The relevance of these data to clinical decision-making was illustrated by letters from several eminent gastroenterologists, with comments such as '5-ASA preparations are special in that the release characteristics are different for the different preparations and very few of them are interchangeable'; copies of the letters were provided.

As Procter & Gamble did not claim an effect on the clinical outcome, and acknowledged Ipocol's place in the management of ulcerative colitis, the company did not believe that it was required to provide data to demonstrate the relationship between *in vitro* data and the clinical situation. Podolsky was cited to support the assertion that it was common practice to select a 5-ASA therapy on the basis of the site of disease. It was not intended to justify an extrapolation to the clinical situation.

Lagap implied that Procter & Gamble had attempted to justify extrapolation. For clarity, the full statement used by Procter & Gamble in intercompany correspondence with Lagap was, 'The theoretical link between *in vitro* and clinical data is widely accepted, but it is important to recognise the limitations of this approach'. This was in the context of a rejection of Lagap's allegation that it had extrapolated to the clinical situation.

Procter & Gamble therefore refuted the allegation that use of *in vitro* data constituted extrapolation to the clinical situation.

PANEL RULING

The Panel noted that the letter was headed 'Switching of mesalazine 400mg preparations'. The letter discussed the reason as to why it was important to ensure that patients already on Asacol continued to receive that brand and were not inadvertently switched to Ipocol. The penultimate paragraph on page one discussed the different *in vitro* release characteristics of Asacol and Ipocol stating that this 'may have implications for the common practice of targeting release of mesalazine based on the site and extent of a patient's disease'.

Appended to the letter was a page headed '*In vitro* dissolution testing of Asacol and Ipocol tablets' which discussed the products' *in vitro* dissolution profiles in pH 7.2 and pH 6.4. The final paragraph read '… the dissolution profile of a mesalazine formulation mediates the site of release and hence the ultimate colonic concentration. The colonic mucosal concentration of mesalazine has been correlated with clinical effect. … Asacol and Ipocol have different release characteristics at both pH 6.4 and pH 7.2'.

The Panel noted that the British National Formulary, March 2003 stated that the 'delivery characteristics of enteric coated mesalazine preparations may vary; these preparations should not be considered interchangeable'.

On balance the Panel considered that the letter explained the difference in release characteristics between Asacol and Ipocol and why this difference was important. No clinical advantage was claimed. No breach of Clause 7.2 was ruled.

C Advertisement

A two page advertisement which took the form of an advertorial appeared in the Pharmaceutical Journal, 30 November 2002, headed 'Management of Ulcerative Colitis The Role of the Pharmacist'.

A graph compared the dissolution results of Asacol and Ipocol, expressed as a % of available mesalazine after 1 hour in pH 7.2 buffer. Ipocol released a statistically significant greater percentage of available mesalazine than Asacol at 10, 20 and 30 minutes; $p< 0.0001$. The graph was derived from data on file ASA004, September 2002. The article stated that the graph showed that the rate of release of Ipocol was markedly different from Asacol.

1 Depiction of dissolution data

COMPLAINT

Lagap alleged that the graph depicting data from the *in vitro* comparative dissolution study between Ipocol and Asacol was misleading in breach of Clause 7.8. The graph did not give a clear, fair or balanced view of the matters with which it dealt and misled by its incompleteness.

The study in question had three stages. Tablets were sequentially tested for 2 hours in 0.1M hydrochloric acid, then for 1 hour in pH 6.4 buffer, then for 1 hour in pH 7.2 buffer. Only the last stage of this study, where the differences between Ipocol and Asacol were more noticeable, was published.

The graph, as depicted, implied that an Ipocol tablet only delivered around 70% of the available mesalazine whilst an Asacol tablet delivered close to 100%. This was misleading since Ipocol tablets also delivered 100% of the available mesalazine during the study.

Many people would just glance at an advertisement and would not have the time nor inclination to read and understand all the text associated with it, particularly information provided in a very small font size. Most pharmacists, particularly community pharmacists to whom this advertisement was aimed, would also have little knowledge of dissolution studies, particularly the more complex sequential staged ones such as this.

RESPONSE

Procter & Gamble stated that the objective of this graph, as was clear from the context of the advertisement, was to illustrate the differences between the dissolution profiles of the two tablets. The study in question comprised three stages (using the standard methodology for Asacol as found in the UK Marketing Authorization application), designed to represent conditions in different parts of the gastrointestinal tract. The stages consisted of 2 hours in 0.1M hydrochloric acid, followed by transfer of the tablets into pH 6.4 buffer for 1 hour, with a further hour in pH 7.2 buffer. Measurements were taken at the end of the first two stages, and every 10 minutes during the final stage. The graph presented the results from the final stage. Although Procter & Gamble did not believe that this graph was misleading, it had already revised the relevant data on file, indicating in the title of the graph that these data were from the third of three stages. The data on file was provided.

According to both the Ipocol and Asacol SPCs, the tablet coating was designed to dissolve at pH 7 and above. No release of mesalazine would therefore be expected during the initial 2 hour stage in 0.1M hydrochloric acid, as this would imply a total failure of the tablet coating function. It was therefore reasonable not to discuss the results from this stage, since it would be assumed that neither product would release mesalazine under these conditions.

Again at pH 6.4 no mesalazine release would be expected. However, Ipocol tablets released approximately 27% of the available mesalazine, compared to less than 1% from Asacol (statistically significant difference in median release, $p< 0.0001$). The remaining mesalazine from each was released in the final stage, at pH 7.2. Both the results at pH 6.4 and those at pH 7.2 supported the conclusion that the *in vitro* dissolution characteristics of Asacol and Ipocol were significantly different from one another. It would therefore not be misleading to show the data from one rather than both of these conditions. However, Procter & Gamble had shown the results from both stages, since the results from the pH 6.4 stage were stated in bullet points below the graph, while the data from pH 7.2 were represented in the graph, thus displaying all relevant information.

The graph showed that Ipocol released around 70% of available mesalazine at the final stage of the *in vitro* analysis. This was because 27% of the mesalazine available had already been released at the previous stage. Although Lagap stated that 100% of available mesalazine was released from Ipocol tablets over the entire experiment, this was not relevant, since the intended point of release (as stated in the Ipocol SPC) was pH 7 and above. It was therefore appropriate to state that 27% of mesalazine was released at pH 6.4, and was not misleading to illustrate that only 70% of it was still available for release at pH 7.2.

All information necessary for the correct interpretation of the graph in question was clearly displayed, giving a clear, fair and balanced view of the data, in line with Clause 7.8 of the Code. Procter & Gamble therefore refuted Lagap's allegation.

PANEL RULING

The Panel noted that the graph was referenced to data on file which summarized *in vitro* dissolution results for Ipocol and Asacol. The study had 3 stages, each mimicking exposure to the pH of the stomach, proximal small bowel and terminal small bowel / proximal colon respectively. Data for the third stage, which mimicked the conditions of that part of the gastrointestinal tract in which Ipocol and Asacol were designed to release mesalazine, was depicted on the graph at issue.

A footnote to the graph read 'Ipocol – at this stage 73% of available mesalazine released following 27% released at pH 6.4. Asacol – at this stage 100% mesalazine released following < 1% at pH 6.4'.

The Panel noted that the advertisement discussed the data on file and the three stage study methodology beneath the heading '*In vitro* dissolution testing'. The products' respective release profiles over the three stages were discussed.

The Panel noted that the graph was clearly labelled 'Dissolution results … after 1 hour in pH 7.2 buffer'; pH 7.2 reflecting the conditions found in the colon and terminal ileum. The Panel considered that within the overall context of the advertisement the graph was not misleading about the products' respective release profiles; sufficient information had been provided about the study methodology. No breach of Clause 7.8 was ruled.

2 Time points

COMPLAINT

Lagap stated that the graph was not accurate and did not reflect the data on file on which it was based, in particular at the 10 minute time point. It should be noted that the data on file ASA004 cited in the advertisement was dated September 2002, whilst the data on file ASA004 supplied to Lagap by Procter & Gamble was dated October 2002.

The graph showed a greater difference between Ipocol and Asacol than the graph depicted in the data on file. Although Procter & Gamble had admitted the error and had said it would rectify it in future, this did not address the issue that Procter & Gamble had misled the reader into believing there was a greater difference between Ipocol and Asacol than actually existed. A breach of Clause 7.2 was alleged.

RESPONSE

Procter & Gamble acknowledged that the graph included an error for one of fourteen data points. This was brought to its attention by Lagap, after which the graph was corrected. In all current materials, the correct version of the graph was used, following steps taken to withdraw and correct materials containing this error.

The difference in impression given between the two graphs was minimal. The correct graph still supported the claim that the *in vitro* dissolution profiles of the two products differed significantly. Procter & Gamble considered that, although one data point was incorrect, the impression given by the graph could not be considered misleading. Procter & Gamble did not consider that this error warranted recourse to the Authority, especially given its response to Lagap, which accepted the error and gave reassurance that it would be corrected for future materials.

PANEL RULING

The Panel noted that on the graph depicted in the data on file the difference in percentage release of available mesalazine between Asacol and Ipocol at 10 minutes was approximately 18%, whilst on the graph in the advertisement it was approximately 52%. The Panel considered the graph misleading in this regard, as acknowledged by Procter & Gamble. A breach of Clause 7.2 was ruled. The Panel noted that Procter & Gamble had withdrawn and corrected materials containing the error and that current materials contained the correct version of the graph.

Complaint received **24 July 2003**

Case completed **23 September 2003**

CASE AUTH/1500/7/03

CROOKES HEALTHCARE v SANKYO PHARMA

Cetraben journal advertisements

Crookes Healthcare alleged that the claim 'No lanolin, no urea, no peanut oil. No problem!', which appeared in two journal advertisements for Cetraben Emollient Cream (white soft paraffin and light liquid paraffin) issued by Sankyo Pharma, disparaged the medicines and products of other pharmaceutical companies. Crookes Healthcare's own product, E45 Cream, contained highly purified, medical grade lanolin and was not associated with lanolin sensitivity. Any implication that problems might be associated with the use of E45 Cream was disparaging and misleading. Crookes Healthcare noted that it also had a range of products which contained urea, which was found naturally in the skin where it was one of the so-called 'natural moisturising factors'. Crookes Healthcare alleged that the claim therefore also disparaged products containing urea.

The Panel noted that some patients might be sensitive to lanolin, urea or peanut oil but considered that the claim 'No lanolin, no urea, no peanut oil. No problem!' went beyond highlighting the sensitivity of a subgroup of patients to these ingredients and suggested that products containing such ingredients were problematic *per se* and that was not so. The claim was disparaging in this regard and a breach of the Code was ruled.

Crookes Healthcare alleged that the claim was also misleading in that it implied that Cetraben was free of problems because it did not contain the ingredients mentioned. This was not true; the Cetraben summary of product characteristics (SPC) stated that the contraindications were 'Hypersensitivity to any of the ingredients' and that the undesirable effects were 'Very rarely, mild allergic skin reactions including rash …'. To claim that Cetraben had 'No problem' was misleading and also an absolute statement and guarantee which could not be substantiated.

The Panel considered that the claim 'No lanolin, no urea, no peanut oil. No problem!' was exaggerated and all embracing; it gave the impression that Cetraben was safe, without qualification or explanation and that no sensitivity issues whatsoever would arise. That was not so. Breaches of the Code were ruled.

Crookes Healthcare further stated that the advertisements were misleading because they did not mention that Cetraben contained butylparaben, methylparaben, ethylparaben and propylparaben. The parabens, as a group, were well known to be potential sensitisers. It was misleading to criticise the ingredients of other products, while not pointing out the composition of its own.

The Panel noted its comments and rulings above but did not consider that inclusion of a statement to the effect that Cetraben contained parabens would have negated the otherwise misleading impression given by the claim 'No lanolin, no urea, no peanut oil. No problem!'. The Panel thus did not consider it was misleading not to state that Cetraben contained parabens and no breach was ruled on this narrow point.

Crookes Healthcare Limited complained about two journal advertisements (refs CTF0307T and CTF0308T) for Cetraben Emollient Cream (white soft paraffin and light liquid paraffin) issued by Sankyo Pharma UK Ltd. Both advertisements had appeared in GP, 23 June. Discussion between the parties had failed to resolve the issues.

Both advertisements featured the headline claim 'No lanolin, no urea, no peanut oil. No problem!'. One advertisement (ref CTF0307T) featured a photograph of a young baby while the other (ref CTF0308T) featured a photograph of three older women. The strapline to each read 'Specially formulated to relieve eczema and dry skin conditions'.

1 Alleged disparagement

COMPLAINT

Crookes Healthcare alleged that the claim 'No lanolin, no urea, no peanut oil. No problem!' disparaged the medicines and products of other pharmaceutical companies in breach of Clause 8.1 of the Code. Crookes Healthcare's own product, E45 Cream, contained lanolin of a highly purified, medical grade and was not associated with lanolin sensitivity. The company could demonstrate that belief in the existence of so-called 'lanolin sensitivity' was based on a misleading study report dating back many years, which had since been misinterpreted by many doctors and nurses. E45 Cream had an excellent safety profile, and any implication that problems might be associated with its use was disparaging and misleading.

Crookes Healthcare noted that it also had a range of licensed products which contained urea, which was found naturally in the skin where it was one of the so-called 'natural moisturising factors'. Crookes Healthcare alleged that the claim was therefore also disparaging to the products containing urea made by it and other manufacturers, and was again a breach of Clause 8.1.

RESPONSE

Sankyo did not agree that the claim 'No lanolin, no urea, no peanut oil. No problem!' disparaged specific products. The company considered that there was a problem for prescribers and patients to any one of these ingredients (in any way) and that by using a product that did not have these ingredients, in the context of this statement there was 'no problem'. Sankyo did not claim that there were 'no problems' with Cetraben Emollient Cream *per se*. The prescribing information stated that the undesirable effects of Cetraben were 'very rare' and were clear to the prescriber.

Sankyo stated that the issue of lanolin sensitivity was well-known not just in dermatological circles but in

the medical profession as a whole. Crookes Healthcare undermined the medical profession when it stated that doctors and nurses had misinterpreted the whole concept of 'lanolin sensitivity' based on a single study report from 1953. Sankyo acknowledged that since then purified grades of lanolin which had a lower sensitivity ie were hypoallergenic (as used in E45 Cream) had become available, however it was inaccurate to suggest that such products were not associated with sensitivity at all. The current summary of product characteristics (SPC) for E45 Cream, which contained a type of hypoallergenic lanolin, Medilan, stated that E45 Cream should not be used by any patients who were 'sensitive to any of the ingredients' and 'occasionally hypersensitivity reactions … should they occur take the form of an allergic rash. Should this occur use of the product should be discontinued'. This suggested that even with purified forms of lanolin a problem still existed. Sankyo noted that the claim in question did not make reference to Medilan or any other type of hypoallergenic lanolin.

The current British National Formulary (BNF) referred to lanolin sensitivity and stated (as suggested above) that purified versions had reduced the extent of this problem but whilst Sankyo acknowledged that to be the case the problem still existed and standard references such as Martindale, Merck Manual, MIMS and the Handbook of Pharmaceutical Excipients continued to report the problem. The National Prescribing Centre, through the MeReC Bulletin, suggested that lanolin and even purified lanolin should be avoided in eczematous patients. Patch tests with refined lanolin and standard wool fat (lanolin) had continued to show sensitivity type reactions. In recent studies lanolin sensitivity had been reported from 0.9-2.3% of patients, 4.4% to as high a prevalence of 12.1% in children with dermatitis. In 36,070 patients tested with lanolin, sensitivity was shown to be much more common in the elderly, particularly in the presence of lower leg dermatitis. Sankyo submitted that the claim of the absence of lanolin and a lanolin associated problem was therefore a valid statement.

Sankyo acknowledged that urea was a commonly used ingredient and was generally considered safe, but considered that it had not suggested otherwise. Urea had been associated with irritancy, stinging or burning and an odour on application, this was the problem for patients as this was not noted with Cetraben. Furthermore high plasma concentrations of urea had been reported following topical application of emollient creams containing urea due to absorption through the skin in neonates. It was also known that urea and urea based excipients used as preservatives ie imidurea, diazolidinylurea had been associated with sensitisation.

Lack (2003) considered a geographically defined cohort study of 13,971 pre-school children and the effects of peanut (arachis) oil in this group. Results showed a significant independent relationship between peanut allergy and the use of skin preparations containing peanut oil (odds ratio, 6.8; 95 percent confidence interval, 1.4 to 32.9) and sensitisation to peanut protein occurred in children through the application of peanut oil to inflamed skin. It had previously been reported that preparations containing arachis oil including topical preparations might pose a risk of hypersensitivity although this was proposed to be minimised by use of refined peanut oil. Sankyo considered that prescribers would be interested to know that Cetraben did not contain peanut oil.

Sankyo noted that no competitor product was mentioned directly or by implication and therefore disagreed that it had disparaged other products or their manufacturers. In some cases opinions might differ but Sankyo considered that it was imperative that these issues were further raised and addressed. It was also a fact that enquiries to the company following publication of Lack had requested details of the absence of such ingredients in Cetraben Emollient Cream from users (doctors, pharmacists and patients).

PANEL RULING

Clause 8.1 stated that the medicines, products and activities of other pharmaceutical companies must not be disparaged. The supplementary information to Clause 8.1 noted that unjustified knocking copy in which the products or activities of a competitor were unfairly denigrated was prohibited.

The Panel noted that some patients might be sensitive to lanolin, urea or peanut oil. The Panel considered that the claim 'No lanolin, no urea, no peanut oil. No problem!' went beyond highlighting the sensitivity of a subgroup of patients to these ingredients and suggested that products containing such ingredients were problematic *per se* and that was not so. The claim was disparaging in this regard. A breach of Clause 8.1 was ruled.

2 Alleged misleading claim

COMPLAINT

Crookes Healthcare alleged that the claim was also misleading in that it implied that Cetraben was free of problems because it did not contain the ingredients mentioned. This was not true; the Cetraben SPC stated that the contraindications were 'Hypersensitivity to any of the ingredients'. Furthermore, under the heading 'Undesirable Effects', it was stated that, 'Very rarely, mild allergic skin reactions including rash and erythema have been observed, in which case use of the product should be discontinued'. To claim that Cetraben had 'No problem' was therefore not only misleading, but was also an absolute statement and guarantee which could not be substantiated. Crookes Healthcare alleged breaches of Clauses 7.9, ('must not be stated that a product has no side effects, …') and 7.10 ('exaggerated and all-embracing claims').

Crookes Healthcare further stated that the advertisements were misleading because they did not mention that Cetraben contained butylparaben, methylparaben, ethylparaben and propylparaben. The parabens, as a group, were well known to be potential sensitisers, and many patients had to avoid

products containing them. While Crookes Healthcare expected that Sankyo had evidence of an acceptable safety profile, it was misleading to criticise the ingredients of other products, while not pointing out the composition of its own. This was alleged to be in breach of Clause 7.10 of the Code which stated that 'Claims should not imply that a medicine or an active ingredient has some special merit, quality or property unless this can be substantiated'.

RESPONSE

Sankyo disagreed that the claim was misleading. The company did not claim that Cetraben was free of problems and indeed the prescribing information included a warning that sensitivity could occur rarely. Sankyo submitted that it was simply stating that Cetraben did *not* contain lanolin, urea or arachis oil and therefore with regard to these ingredients there was no problem. Sankyo therefore submitted that the claim in question was a statement of fact and not a claim that Cetraben was free from side effects. The specificity of the claim was such that Sankyo did not agree that it was all-embracing. Furthermore the proximity of the first half of the claim 'No lanolin, no urea, no peanut oil' to the second half 'No problem!' clearly, in Sankyo's view, linked the two.

Sankyo noted that Crookes Healthcare had cited the presence of parabens in Cetraben as the reason why it could not claim that Cetraben had 'no problems'. As had been explained this was not what Sankyo was claiming although sensitivity to Cetraben was rare. The details were contained in the prescribing information and prescribers were expected to refer to the SPC before prescribing as was usual practice.

The Food and Drug Administration rated methyl and propyl parabens as second only to water as the most commonly found ingredients in cosmetics. The hydroxybenzoates or parabenzoates as a group were the most widely used preservatives in cosmetics, methyl parabenzoate being the most used followed by propyl parabenzoate. Given the widespread use of parabenzoates as preservatives in cosmetics, pharmaceuticals and food products, allergic reactions were relatively uncommon. The reported sensitivity level in a 10 year overview (1991-2000) to parabens was the lowest of all preservatives being in the range of 0.5-1%.

Sankyo stated that the headline claimed that Cetraben did not contain three ingredients commonly found in topical preparations (fact) and that any such problem commonly associated with these ingredients was avoided with Cetraben (fact). The company did not consider that the claim therefore provided or implied any special merit which was unsubstantiated.

PANEL RULING

The Panel noted that Section 4.3 of the Cetraben SPC, Contra-indications, stated 'Hypersensitivity to any of the ingredients'. Section 4.4, Special Warnings and Precautions for Use, stated 'None known'. Section 4.8 Undesirable Effects stated 'Very rarely, mild allergic skin reactions including rash and erythema have been observed …'. The Panel considered that the claim 'No lanolin, no urea, no peanut oil. No problem!' was exaggerated and all embracing; it gave the impression that Cetraben was safe, without qualification or explanation and that no sensitivity issues whatsoever would arise. That was not so. Breaches of Clauses 7.9 and 7.10 were ruled.

The Panel noted its comments and rulings above but did not consider that inclusion of a statement in the advertisement to the effect that Cetraben contained parabens would have negated the otherwise misleading impression given by the claim 'No lanolin, no urea, no peanut oil. No problem!'. The Panel thus did not consider it was misleading not to state that Cetraben contained parabens and no breach of Clause 7.10 was ruled on this narrow point.

Complaint received **25 July 2003**

Case completed **17 September 2003**

CASE AUTH/1501/8/03

BRISTOL-MYERS SQUIBB and SANOFI-SYNTHELABO v SANKYO PHARMA

Olmetec leavepiece

Bristol-Myers Squibb and Sanofi-Synthelabo complained about an Olmetec (olmesartan) leavepiece issued by Sankyo Pharma. Olmetec was an angiotensin II antagonist. Bristol-Myers Squibb and Sanofi-Synthelabo supplied Aprovel (irbesartan).

The complainants referred to the claim 'Up to 46% greater reduction in DBP than losartan 50mg, valsartan 80mg and irbesartan 150mg by week 8' and noted that according to the reference (Oparil *et al* 2001) this reduction clearly related to the advantage over losartan. The reduction in comparison with irbesartan was only 14%. It was alleged that the claim was thus misleading.

The Panel considered that the claim 'Up to 46% greater reduction in DBP than losartan 50mg, valsartan 80mg and irbesartan 150mg by week 8' implied that Olmetec produced a 46% greater reduction in DBP than all of the other products mentioned. This was not so. The Panel further noted that use of the phrase 'up to' seldom negated the impression that the maximum result was achieved in every case; the 46% greater reduction was only achieved when Olmetec was compared with losartan. The Panel considered that the claim was misleading as alleged. Breaches of the Code were ruled.

Bristol-Myers Squibb Pharmaceuticals Limited and Sanofi-Synthelabo Limited complained about the promotion of Olmetec (olmesartan) by Sankyo Pharma UK Ltd. The material at issue was a leavepiece (ref OLM 16.1). Olmetec was an angiotensin II antagonist. Bristol-Myers Squibb and Sanofi-Synthelabo supplied Aprovel (irbesartan).

Claim 'Up to 46% greater reduction in DBP than losartan 50mg, valsartan 80mg and irbesartan 150mg by week 8'

COMPLAINT

Bristol-Myers Squibb and Sanofi-Synthelabo noted that, according to the paper quoted (Oparil *et al* 2001), this reduction clearly related to the advantage over losartan. The reduction in comparison with irbesartan was considerably less (14%). The complainants alleged that this generalisation was thus a misrepresentation of the data with the intention to mislead. As a result of this doctors might erroneously believe that Olmetec was 46% more effective than irbesartan and thus initiate a switch in medication. This would clearly not be in the interest of the patient as other treatment options might be more appropriate, such as the addition of another agent. Breaches of Clauses 7.2 and 7.3 were alleged.

RESPONSE

Sankyo stated that the inclusion of the words 'up to' meant that not all the included products were the same. Clearly one or more would be 46% but the others would obviously be less as the 46% indicated the maximum. In Sankyo's view, the claim did not mean that Olmetec produced greater diastolic blood pressure (DBP) reduction than all the other products included at 46%. The products were deliberately listed with the product with the least difference in reduction (irbesartan) last.

A table in Oparil *et al* clearly stated the differences from which the percentages had been calculated and there was no discrimination made against any one product. The figures used were the least squares mean change from baseline in DBP after 8 weeks of treatment as this was the primary efficacy variable of the study; the difference was 46% for valsartan, 40% for Iosartan and 16% for irbesartan.

Sankyo submitted that there was 'Up to 46% greater reduction in DBP than losartan, valsartan and irbesartan by week 8'.

In addition a sales aid used by the representative further quantified the level of reduction by providing a graphical representation of the reduction at week 8 in mmHg and then the individual percentage reductions by product.

In summary, Sankyo stated that the leavepiece was simply a summary of data and could not be all encompassing. It was always provided personally by a sales representative with supporting data where appropriate. The full reference could be provided if requested by the doctor.

Sankyo denied breaches of Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel noted Sankyo's submission that the leavepiece was a summary of the data which was always provided personally by a sales representative, with supporting data where appropriate, and that a copy of Oparil *et al* could be provided if the doctor requested it. Sankyo had also stated that the sales aid used by the representatives further quantified the data and provided a graph showing the reductions in DBP at week 8 for each product. The Panel noted, however, that it was an accepted principle under the Code that each piece of promotional material must be regarded as a stand alone item and comply with the Code in its own right without the need to rely on other material for it so to do.

The Panel considered that the claim 'Up to 46% greater reduction in DBP than losartan 50mg, valsartan 80mg and irbesartan 150mg by week 8' implied that Olmetec produced a 46% greater reduction in DBP than all of the other products

mentioned. This was not so. The Panel further noted that use of the phrase 'up to' seldom negated the impression that the maximum result was achieved in every case; the 46% greater reduction was only achieved when Olmetec was compared with losartan. The Panel considered that the claim was misleading as alleged. Breaches of Clauses 7.2 and 7.3 were ruled.

Complaint received **4 August 2003**

Case completed **9 September 2003**

CASE AUTH/1502/8/03

NOVO NORDISK v ORION PHARMA

Promotion of Indivina

Novo Nordisk complained about a leavepiece and a journal advertisement for Indivina (oestradiol valerate (E_2V) and medroxyprogesterone acetate (MPA)) issued by Orion Pharma. Indivina, a continuous combined hormone replacement therapy (HRT), was available in three dose combinations: 1mg E_2V/2.5mg MPA, 1mg E_2V/5mg MPA and 2mg E_2V/5mg MPA. Novo Nordisk alleged that the claims 'At 6 months: 9 out of 10 women are still maintained on the lowest dose of Indivina' (leavepiece) and '9 out of 10 women on Indivina are still maintained on the lowest dose at 6 months' (advertisement) were ambiguous and misleading and could not be substantiated by the references used to support them (Heikkinen *et al* 2000 and Bruhat *et al* 2001). The claims implied that there was a clinical benefit to the women by staying on the lowest dose of Indivina whereas they did so because it was part of the methodology of both studies. There was no clinical assessment as to whether each patient would benefit from an increase in the dosage of their therapy.

Novo Nordisk supplied a number of hormone replacement therapy products.

The Panel noted that in the leavepiece the claim 'At 6 months: 9 out of 10 women are still maintained on the lowest dose of Indivina' appeared beneath a diagram in which prescribers were advised to start with the lowest dose of Indivina and that this dose should be continued unless climacteric symptoms occurred, in which case a higher dose should be prescribed (2mg E_2V/5mg MPA), or breakthrough bleeding occurred when 1mg E_2V/5mg MPA should be used. Beneath the diagram was the claim '3 simple doses allow you to adjust her dose depending on her needs'. The Panel noted Orion's submission that 'still maintained' had been used in the sense of 'to continue or retain; keep in existence'. The Panel noted that 'maintain' was also defined as 'guard from loss or deterioration'. In the context in which it appeared the Panel considered that the claim at issue implied that at 6 months 9 out of 10 women were maintained on the lowest dose of Indivina in that they had had neither a recurrence of climacteric symptoms nor any breakthrough bleeding ie there had been no clinical need to adjust the dose. This was not necessarily so. The Panel considered that the claim was misleading in that regard and could not be substantiated. Breaches of the Code were ruled.

The advertisement referred to the three dose combinations of Indivina and stated that 'Indivina simply allows you to adjust her dose, depending on her needs'. This was followed by the claim '9 out of 10 women on Indivina are still maintained on the lowest dose at 6 months'. As with the claim in the leavepiece the Panel considered that the claim at issue was misleading and could not be substantiated. Breaches of the Code were ruled.

Novo Nordisk Limited complained about the promotion of Indivina (oestradiol valerate (E2V) and medroxyprogesterone acetate (MPA)) by Orion Pharma (UK) Ltd. Indivina was available in three dose combinations: 1mg E_2V/2.5mg MPA, 1mg E_2V/5mg MPA and 2mg E_2V/5mg MPA. The material at issue was a leavepiece (ref HRT0822) which had been used in primary and secondary care between 14 April and 30 June and an advertisement (ref IND0794) which had appeared in the GP press between 19 May and 16 June 2003. Indivina was a continuous combined hormone replacement therapy (HRT).

Novo Nordisk supplied a number of hormone replacement therapy products.

'At 6 months: 9 out of 10 women are still maintained on the lowest dose of Indivina'

This claim appeared in the leavepiece.

'9 out of 10 women on Indivina are still maintained on the lowest dose at 6 months'

This claim appeared in the advertisement.

Both claims were referenced to Heikkinen *et al* (2000) and Bruhat *et al* (2001).

COMPLAINT

Novo Nordisk alleged that the claims breached Clauses 7.2 and 7.4 since they were ambiguous and misleading according to the references used to support them. Bruhat *et al* stated that women were randomised to one of three treatment groups to receive: 1mg E_2V/2.5mg MPA and 1mg E_2V/5mg MPA for the first 6 months, thereafter E_2V dose was increased to 2mg in both groups (groups E_2V/MPA 2.5 and E_2V/MPA 5). The reason that women were on the lowest dose at 6 months was because the design of the study specified this. The claim that 9 out of 10 women were maintained on the lowest dose at 6 months implied that they did not need a higher dose. These references therefore did not support the claims since the study protocols did not incorporate a clinical assessment as to whether each patient would benefit from an increase in the dosage of their HRT.

Heikkinen *et al* had six treatment groups;

1mg E_2V/2.5mg MPA (months 0-6); increased to 2mg E_2V/2.5mg MPA (months 7-48) – Group A

1mg E_2V/5mg MPA (months 0-6); increased to 2mg E_2V/5mg MPA (months 7-48) – Group A

2mg E_2V/2.5mg MPA (months 0-48) – Group B

2mg E_2V/5mg MPA (months 0-48) – Group B

1mg E_2V/2.5mg MPA (months 0-48) – Group C

1mg E_2V/5mg MPA (months 0-48) – Group C

As with Bruhat *et al*, the study protocol actually specified women to be on the low dose 1mg E_2V/2.5mg MPA for 6 months as shown by 'in two groups the low dose of 1mg E_2V was raised to 2mg after the initial 6 months of treatment'. The doses were increased after 6 months primarily to compare the bleeding patterns and the protocol was not designed to assess whether or not patients would have benefited from an increase in their dosage earlier than 6 months. In addition, Orion had used the continuation rates of the study to reflect patients being maintained on their dose. However, people dropped out of a study for all sorts of reasons which might not have anything to do with their medication. Also, patients were often more likely to comply with their medication in a study than in a real life situation because they were being more closely monitored. Novo Nordisk considered that it was misleading to use the continuation rates of such rigid protocol studies to substantiate the claims and that this did not reflect a real-life scenario.

According to both Bruhat *et al* and Heikkinen *et al*, the claim '9 out of 10 women are still maintained on the lowest dose at 6 months', was not only unsubstantiated but it was also misleading in that it implied that there was a clinical benefit to the women by staying on the lowest dose of Indivina, not that it was part of the methodology.

RESPONSE

Orion stated that Bruhat *et al* randomized women to one of three treatments (1mg E_2V/2.5mg MPA, 1mg E_2V/5mg MPA or 2mg E2 [micronised estradiol]/1mg NETA [norethisterone acetate]) for the first 6 months of the study. After 6 months the dose of E_2V was increased to 2mg in both the E_2V/MPA groups. The Kaplan-Meier graph in the published paper showed that the proportion of patients remaining in the study at 168 days (24 weeks) in the 1mg E_2V/2.5mg MPA arm was approximately 0.9 (ie 90%).

Heikkinen *et al* randomized patients to one of six treatment regimens. For the first six months patients in two of these treatment groups received 1mg E_2V/2.5mg MPA; in one of these groups treatment was increased to 2mg E_2V/2.5mg MPA after 6 months. Heikkinen *et al* described the study design and results for treatment groups pooled by E_2V dose. Unpublished data from the study showed that the continuation rates at 6 months were 91.4% and 94.2% for the two groups on 1mg E_2V/2.5mg MPA.

Orion disagreed with Novo Nordisk's assertion that the claims implied that the women studied did not need a higher dose of treatment during the first six months when the design of the studies did not permit an assessment earlier than 6 months to assess whether the patients would need a higher dose. The company also disagreed that the claims implied that there was a clinical benefit to the women by staying on the lowest dose of Indivina, not that it was part of the study methodology.

The Collins English Dictionary defined 'maintain' as 'to continue or retain; keep in existence' and this was the sense in which 'still maintained' had been used. It did not imply that the women did not need a higher dose or that they experienced a clinical benefit from staying on the lower dose. The claim simply described the number of women who were still on treatment at the end of six months. Treatment-associated bleeding was a well recognized cause of poor compliance in women taking HRT; Bruhat *et al* stated 'If bleeding during the early months of therapy can be reduced or eliminated, compliance with therapy is likely to be improved'. Both Bruhat *et al* and Heikkinen *et al* showed that 1mg E_2V/2.5mg MPA was associated with a low level of breakthrough bleeding. There was no implication that women had better symptom control on this dose than they might have had on any other dose – the studies were not designed to assess this. However there was no significant difference in symptom control at 6 months between any of the treatment groups in Bruhat *et al* or between women on low and high dose oestrogen regimens in Heikkinen *et al*.

Orion noted Novo Nordisk's allegation that the claims were misleading as the results of the studies did not reflect a real life scenario. In fact the design of both studies reflected current prescribing practice in that women attended for a clinic assessment after three months of treatment. At this assessment the patients' symptoms and bleeding pattern were reviewed. As was the case in any trial, this assessment provided an opportunity for patients and investigators to consider whether treatment should be continued.

In summary, Orion submitted that the claim '9 out of 10 women on Indivina are still maintained on the lowest dose at 6 months' was adequately supported by Bruhat *et al* and Heikkinen *et al*, that it was clear, unambiguous and not misleading and was therefore not in breach of Clauses 7.2 and 7.4 of the Code.

PANEL RULING

The Panel noted that of the six patient groups in Heikkinen *et al*, the study protocol had dictated that one (n=70) had taken 1mg E_2V/2.5mg MPA (ie the lowest dose of Indivina) for months 0-6 after which the dose of E2V was increased to 2mg for months 7-48. Another patient group (n=69) had taken the lowest dose of Indivina for months 0-48. Patients were assessed at months 6, 12, 24, 36 and 48 (patients were not reviewed at 3 months as submitted by Orion). Orion had provided unpublished data from the study to show that at 6 months 91.4% and 94.2% of patients respectively were still in the study.

The study protocol of Bruhat *et al* had similarly dictated that patients in one of the treatment groups should take the lowest dose of Indivina for months 0-

6 before having the E_2V dose increased to 2mg in months 7-12. Patients were assessed at 3, 6, 9 and 12 months. From a figure in the paper it could be estimated that at 6 months 90% of patients remained in the low dose group.

The Panel noted that in both studies patients could discontinue if they wished but in neither case could their therapy be changed before 6 months. Patients in Heikkinen *et al* were not assessed before month 6 and those in Bruhat were not assessed before month 3.

The Panel noted that in the leavepiece the claim 'At 6 months: 9 out of 10 women are still maintained on the lowest dose of Indivina' appeared beneath a diagram in which prescribers were advised to start with the lowest dose of Indivina and that this dose should be continued unless climacteric symptoms occurred, in which case a higher dose should be prescribed (2mg E_2V/5mg MPA), or breakthrough bleeding occurred when 1mg E_2V/5mg MPA should be used. Beneath the diagram was the claim '3 simple doses allow you to adjust her dose depending on her needs'. The Panel noted Orion's definition of 'maintain'. It was also defined as 'guard from loss or deterioration'. In the context in which it appeared the Panel considered that the claim at issue was more than a claim for patient compliance; it implied that at 6 months 9 out of 10 women were maintained on the lowest dose of Indivina in that they had had neither a recurrence of climacteric symptoms nor any breakthrough bleeding ie there had been no clinical need to adjust the dose. This was not necessarily so. The Panel considered that the claim was misleading in that regard and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

The advertisement referred to the three dose combinations of Indivina and stated that 'Indivina simply allows you to adjust her dose, depending on her needs'. This was followed by the claim at issue '9 out of 10 women on Indivina are still maintained on the lowest dose at 6 months'. Again the Panel considered that the claim implied that there had been no clinical need to adjust the dose of Indivina over the 6 month period and this was not necessarily so. The Panel considered that the claim was misleading and could not be substantiated. Breaches of Clauses 7.2 and 7.4 were ruled.

Complaint received **4 August 2003**

Case completed **16 September 2003**

CASE AUTH/1503/8/03

GENERAL PRACTITIONER v LEO PHARMA

Sponsored journal

A general practitioner complained that he had received an eight page journal, Psoriasis in Practice, from a medical communications agency which in reality appeared to be a promotional mailing from Leo. The complainant noted that an article, entitled Treatment of plaque psoriasis in the community, included a psoriasis decision tree, devised by the Psoriasis Working Party, which had Dovobet [Leo's product] in the bull's eye position. The article appeared to have come from Leo's marketing department, a view supported, *inter alia*, by the statement that the working party was 'charged with producing a primary care treatment that incorporates Dovobet as an option'. Allusions to the British Association of Dermatologists (BAD) suggested that the information in the article was in accord with its guidelines which was not so. An advertisement for Dovobet appeared on the back page. At the foot of the second page was a statement that Psoriasis in Practice was supported by an educational grant from the Leo Foundation.

The Panel noted that it was acceptable for companies to sponsor material, the content of which 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. A company could 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.

Psoriasis in Practice had been sponsored by Leo which had been able to influence the choice of authors and subject matter. The third and final article, Treatment of plaque psoriasis in the community, referred to the psoriasis decision tree devised by the Psoriasis Working Party. Dovobet appeared in prime position in the decision tree and was described in the article as a first line therapy. The Psoriasis Working Party was sponsored by Leo. The outside back cover was an advertisement for Dovobet.

The Panel considered that Leo was inextricably linked to the production of the particular issue of Psoriasis in Practice in question. There was no arm's length arrangement between the provision of sponsorship and the generation of the document. Given Leo's involvement and the content of the material the Panel considered that the issue of Psoriasis in Practice in question was an eight page promotional mailing for Dovobet and this was the basis on which it made its rulings.

The Panel noted that prescribing information had been provided on the outside back cover. No breach of the Code was ruled in that regard. The Code required printed promotional material of more than four pages to include a clear reference as to where the prescribing information could be found. Although such a reference was given at the end of the third article the Panel considered that its

location was such that a clear reference had not been provided. A breach of the Code was ruled.

The Panel considered, given the way in which the mailing had been produced, that the statement that Psoriasis in Practice was supported by an educational grant from Leo gave a misleading impression of the company's role in the generation of the document. The journal was promotional material paid for by Leo. A breach of the Code was ruled. The declaration of Leo's sponsorship was printed on page 2. In the Panel's view this did not satisfy the requirement in the Code that readers should be aware of a company's involvement at the outset. A breach of the Code was ruled.

The Panel considered that the mailing was presented in such a way that many readers would assume that it was an independently produced medical journal which was not so. The reference to an educational grant from Leo added to that impression as did the fact that the mailing had been sent by a medical communications agency. The promotional nature of the document had been disguised. The Panel ruled a breach of the Code.

The Panel considered that although the article, Treatment of plaque psoriasis in the community, referred to the BAD and discussed the role of Dovobet, it was clear that the decision to place Dovobet at the centre of the psoriasis decision tree was to reflect the views of the Psoriasis Working Party. Recommendations within the article about who should treat psoriasis accorded with the BAD recommendations. The Panel did not consider that the article was inconsistent with the BAD recommendations. No breach of the Code was ruled.

Overall, the Panel considered that Leo's involvement in the production of a promotional mailing, disguised to look like an independent medical journal, meant that high standards had not been maintained. A breach of the Code was ruled.

A general practitioner complained about the involvement of Leo Pharma in the production of an eight page journal Psoriasis in Practice, Volume 2 Number 1, 2003. The journal had been sent in a plastic wrapper clearly marked from Hayward Medical Communications.

COMPLAINT

The complainant stated that he had received the journal from Hayward Medical Communications in a plastic wrapper which indicated that he was to receive a medical journal rather than a promotional item.

As the subject on the first page (the psychological impact of psoriasis) interested him he read the article and then noted at the foot of the second page that the journal was supported by an educational grant from the Leo Foundation. The complainant continued reading but was surprised to see that the psoriasis decision tree on page 5 had Dovobet [Leo's product] in the bull's eye position. This immediately suggested a promotional piece and he was therefore not surprised to find on reading the article, Treatment of plaque psoriasis in the community, that it appeared to have come from the marketing department for Dovobet. His view was supported by the statement that the Psoriasis Working Party was 'charged with producing a primary care treatment that incorporates Dovobet as an option' and by references to data on file rather than published papers. The allusions to the British Association of Dermatologists (BAD) in the article and references to its website suggested the information in the article was in accord with its guidelines. This was not so. Copies of the relevant extracts from the BAD guidelines were provided. If, as the complainant considered, this publication was promotional in its entirety, he was sure there was further material within the publication, which was contrary to the Code.

Prescribing information and an advertisement for Dovobet eventually appeared on the back page. The complainant had not sought information from Leo to substantiate the claims made in the advertisement as once again he noted it was data on file. Nor had he sought a copy of the educational module advertised to ascertain whether it could also be regarded as promotional.

The complainant stated that the substance of his concern was that in the first instance he was misled as to the nature of the publication and secondly that the promotional material within the publication appeared to be in breach of the Code.

When writing to Leo the Authority asked it to respond in relation to Clauses 4.1, 4.7, 4.8, 6.3, 7.2, 7.4, 9.1, 9.10 and 10.1 of the Code. The case was considered according to the requirements of the 2003 edition of the Code.

RESPONSE

Leo stated that Psoriasis in Practice was neither a promotional item nor was it disguised promotion. It was one of a range of In Practice journals produced by Hayward and sponsored by a number of pharmaceutical companies. Leo's sponsorship of Psoriasis in Practice was clearly acknowledged on page 2 of the journal. Leo stated that it had an arm's length relationship with Hayward and had no editorial control. As sponsors, Leo approved the journal prior to publication to ensure that no criticism could be levelled at Leo in respect of bias in favour of Leo or of its products.

Leo stated that it was hardly surprising that its products featured from time to time given their significance in the treatment of psoriasis. However, in the issue in question, in seven pages of text only two pages and one paragraph related to a Leo product, Dovobet.

Leo submitted that the complainant had clearly misunderstood the reference to the BAD in the article 'Treatment of plaque psoriasis in the community'. This reference concerned national guidelines on referral advice and did not, either directly or implicitly, indicate the position of Dovobet in any treatment paradigm. Indeed such a suggestion would not be credible given that the BAD guidelines in question predated the introduction of Dovobet.

Because of the significant impact of Dovobet in the treatment of psoriasis since its introduction in May 2002, it was reasonable that dermatologists and GPs should seek to recommend where the product should be aligned within these pre-existing BAD guidelines. The Psoriasis Working Party comprised seven dermatologists and specialist GPs. The psoriasis decision tree was the result of their deliberations. In Leo's view the author and his colleagues on the working party would take a dim view of the allegation that the paper was written by 'the marketing department for Dovobet'.

Leo noted that there was no specific complaint about the Dovobet advertisement on the back page. If the complainant would like to receive any referenced information or any other information or justification with respect to the advertisement Leo would be happy to oblige. The same applied to the education module (presumably the CPD in dermatology referred to on page 4).

In conclusion, therefore, Leo considered that Psoriasis in Practice was non-promotional in its entirety, with the exception of the Dovobet advertisement on the outside back cover about which no complaint had been made.

In response to a request for further information Leo stated that it sponsored Hayward to produce Psoriasis in Practice. The named authors in the journal wrote the articles which had been edited by Hayward. The authors and subject matter were suggested by both Leo and Hayward through their knowledge of the disease area and the dermatology community.

The prescribing information was only relevant as to the requirement of the Code, as it applied to the advertisement for Dovobet (ref 4264) on the back page. In this position it met all requirements of this clause. The note on page 7 regarding the prescribing information was an editorial comment for the benefit of the reader.

The article, Treatment of plaque psoriasis in the community, was written by the Chairman of the Primary Care Dermatology Society. In the article he presented the psoriasis decision tree, developed by the Psoriasis Working Party. The Psoriasis Working Party was chaired by a consultant dermatologist and sponsored by Leo. The working party was charged with developing an algorithm or decision tree for provision to general practice as a tool to aid GPs in negotiating the treatment pathway when confronted with a patient suffering from psoriasis. Through a series of meetings and other communications it developed the decision tree included in this article – all members of the working party approved the decision tree and they were not influenced in any way by Leo as to which options to include. Psoriasis in Practice was mailed to GPs and dermatologists; no copies had been distributed in any other way.

PANEL RULING

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

The issue of Psoriasis in Practice in question had been sponsored by Leo. Leo had been able to influence the choice of authors and subject matter. The first article discussed the psychological impact of psoriasis whilst the second examined possible new treatments for psoriasis. The third and final article, Treatment of plaque psoriasis in the community, referred to the psoriasis decision tree devised by the Psoriasis Working Party. The article stated that the Psoriasis Working Party was a group of seven specialist dermatologists and GPs charged with producing a primary care treatment that incorporated Dovobet (calcipotriol / betamethasone) ointment as an option. Dovobet appeared in prime position in the decision tree and the article featured a section headed The place of Dovobet and a table of data entitled Dovobet: the evidence. Dovobet was described in the article as a first line therapy. The Psoriasis Working Party was sponsored by Leo and Dovobet was marketed by that company. The outside back cover was an advertisement for Dovobet.

The Panel considered that Leo was inextricably linked to the production of the particular issue of Psoriasis in Practice in question. There was no arm's length arrangement between the provision of sponsorship and the generation of the document. Given the company's involvement and content of the material the Panel considered that the document was in effect promotional material for Dovobet. The item had the general appearance of a medical journal. It had been given a volume and number reference. Part of the front cover highlighted the articles contained within and gave page numbers for each. The first two articles were of a general nature but the third featured a discussion on Dovobet. The outside back cover had the appearance of a journal advertisement. The Panel, however, did not consider that the document in question was a journal in the accepted sense of the word. Given Leo's involvement the Panel considered that the issue of Psoriasis in Practice in question was an eight page promotional mailing for Dovobet and this was the basis on which it made its rulings.

With regard to prescribing information the Panel noted that this had been provided on the outside back cover. No breach of Clause 4.1 was ruled. Clause 4.8 required that, in the case of printed promotional material which consisted of more than four pages, a clear reference must be given as to where prescribing information could be found. Although a reference as to where the prescribing information could be found was given on page 7, at the end of the article entitled 'Treatment of plaque psoriasis in the community', the Panel considered that its location was such that a clear reference had not been provided. A breach of Clause 4.8 was ruled.

The Panel considered, given the way in which the mailing had been produced, that the statement on page 2 that Psoriasis in Practice was supported by an educational grant from Leo gave a misleading impression of the company's role in the generation of the document. The journal was promotional material paid for by Leo. A breach of Clause 7.2 was ruled.

The Panel considered that the mailing was presented in such a way that many readers would assume that it was an independently produced medical journal which was not so. The reference to an educational grant from Leo added to that impression as did the fact that the mailing had been sent by a medical communications agency. The promotional nature of the document had been disguised. The Panel ruled a breach of Clause 10.1 of the Code.

The Panel note that Clause 9.10 of the Code stated that material relating to medicines and their uses, whether promotional in nature or not, which was sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company. The supplementary information to Clause 9.10 stated that the declaration of sponsorship must be sufficiently prominent to ensure that readers of sponsored material were aware of it at the outset. The Panel noted that the declaration of Leo's sponsorship was printed on page 2. In the Panel's view this did not satisfy the requirement that readers should be aware of a company's involvement at the outset. A breach of Clause 9.10 was ruled.

Clauses 4.7 and 6.3 referred to journal advertising; however, the Panel viewed Psoriasis in Practice as an eight page promotional mailing and not as a journal. No breach of Clauses 4.7 and 6.3 was ruled.

The Panel noted that the article, Treatment of plaque psoriasis in the community, stated that although the BAD had released information on specific treatment groups and referral advice, two-thirds of GPs would like more guidance on psoriasis. That need was the spur for the development of the psoriasis decision tree. The other motivation was the expected availability of Dovobet which was described as the first significant breakthrough in the treatment of psoriasis for a decade. The decision tree showed that patients with mild to moderate psoriasis which required treatment could be managed by their GPs with Dovobet. No other therapy option at that point was given. Those patients presenting with moderate to severe psoriasis, and with more than 30-40% coverage, should be referred to a specialist. The recommendations given on who should treat the psoriasis accorded with the recommendation given by the BAD that most patients with mild to moderate plaque psoriasis could be treated by the primary care team using topical therapies. The Panel noted that the BAD made no recommendations about the use of Dovobet *per se*. Dovobet was a topical therapy. The BAD website included pages which discussed topical vitamin D analogues including calcipotriol and also pages which discussed topical corticosteroids. There was no discussion on the role of fixed combination therapy. The Panel considered that although the article in question referred to the BAD and discussed the role of Dovobet it was clear that the decision to place Dovobet at the centre of the psoriasis decision tree was to reflect the views of the Psoriasis Working Party. The Panel did not consider that the article was inconsistent with the BAD recommendations. No breach of Clauses 7.2 and 7.4 was ruled.

Overall, the Panel considered that Leo's involvement in the production of a promotional mailing, disguised to look like an independent medical journal, meant that high standards had not been maintained. A breach of Clause 9.1 was ruled.

The Panel considered that it had not received a complaint about either the back page *per se* of the mailing or the CPD module. No rulings were made with regard to these materials.

Complaint received **6 August 2003**

Case completed **3 October 2003**

CASE AUTH/1504/8/03

PRIMARY CARE TRUST CHIEF EXECUTIVE v JANSSEN-CILAG

Atypical Anti Psychotic Shared Care Guidelines

The chief executive of a primary care trust (PCT) complained about a document sent by a representative of Janssen-Cilag to a prescribing adviser in another PCT. The document, entitled '[named city] Atypical Anti Psychotic Shared Care Guidelines', featured the logos of five PCTs, including that of the complainant, on its front cover and was accompanied by a covering letter from the representative.

The complainant stated that the shared care guidelines had not been approved by any committee within his PCT and he understood that they had been printed by Janssen-Cilag, although there was no mention of this on the document. It would be bad enough if Janssen-Cilag was using approved documentation for promotional purposes without permission, but to be using a document with the complainant's PCT logo on it, which was not approved by the PCT, was not only misleading but threw the industry's reputation into disrepute.

The Panel noted that Janssen-Cilag had not been involved in developing the guidelines. Its only role (together with that of another company) was to pay for the printing of the guidelines. This had not been made clear on the document. A breach of the Code was ruled.

It appeared that the complainant's PCT might not have seen the guidelines; a letter from the complainant to Janssen-Cilag stated that neither the Professional Executive Committee nor the Board of the PCT had approved the document. In the Panel's view this was a communication problem between those drawing up the guidelines and the PCTs and not Janssen-Cilag's responsibility as the company had no role in developing the guidelines.

About two months after the representative had sent the guidelines to the PCT prescribing adviser, the chairman of the group which had drawn up the guidelines wrote to Janssen-Cilag stating that the guidelines were in the public domain. There was no reference in the letter to Janssen-Cilag's use of the guidelines. In the circumstances the Panel did not consider that Janssen-Cilag had received prior written permission to use the document for promotional purposes. The Panel considered that Janssen-Cilag had failed to maintain a high standard. Breaches of the Code were ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

The chief executive of a primary care trust (PCT) complained about material sent by a representative of Janssen-Cilag Ltd to a prescribing adviser in another PCT. The material consisted of a document entitled '[named city] Atypical Anti Psychotic Shared Care Guidelines' and featured on its front cover the logos of five PCTs including that of the complainant. The guidelines were accompanied by a covering letter from the representative.

COMPLAINT

The complainant stated that the shared care guidelines had not been approved by any committee within his PCT, nor had it been printed by his PCT. The complainant understood that the guidelines had been printed by Janssen-Cilag although there was no mention of this on the document.

The complainant stated that it would be bad enough if Janssen-Cilag was using approved documentation for promotional purposes without permission, but to be using a document with his PCT logo on it, which was not approved by the PCT, was not only misleading but threw the industry's reputation into disrepute. Breaches of Clauses 2, 9.6 and 9.10 of the 2003 edition of the Code were alleged. As the distribution of the document was prior to 1 July 2003, it was considered under the 2001 Code and the clauses equivalent to those cited by the complaint were 2, 9.5 and 9.9.

RESPONSE

Janssen-Cilag stated that the guidelines were first developed through 2001 by an Interface Prescribing Group chaired by a consultant psychiatrist in a local mental health trust. The small group, at that stage, consisted of representatives of three PCTs including the complainant's. A treatment algorithm for the medical treatment of adult schizophrenia was developed and published within the chairman's mental health trust in November 2001. Thereafter, with growing interest from the surrounding PCTs, the group expanded and included representation from all the PCTs. It met monthly to discuss the further development of this algorithm and agree on the guidelines now at issue. The representative in question was in frequent contact with senior NHS managers and the NHS representatives on this guidelines development group. The representative's job was to discuss and assist NHS colleagues in gaining a full understanding of the company's product (Risperdal) so that it could be appropriately considered when the guidelines were being drafted.

In April 2003, the Interface Prescribing Group finally agreed the guidelines. By this stage, membership of the group had considerably expanded and included (from late 2002) two representatives of the complainant's PCT. Up to that point Janssen-Cilag had, of course, not been involved with the development of any of these NHS guidelines.

Janssen-Cilag stated that after the representative had seen the prescribing adviser of the PCT and forwarded a copy of the Shared Care Guidelines with an accompanying letter, the prescribing adviser had

sent these to the complainant. Janssen-Cilag provided a copy of a letter from the chairman of the Interface Prescribing Group which had developed the guidelines clarifying the position regarding the distribution and further discussion of these guidelines. The letter clearly noted that the guidelines were in the public domain and had been published in a journal, Medicine Matters, in May 2003. Indeed the chairman additionally noted that he had '… nothing against the guidelines being discussed with other PCTs as this should facilitate sharing best practice ...'. The representative used the permission from the chairman as authority to use that document with other parts of the NHS.

Given that members of the complainant's PCT participated in the Interface Prescribing Group, and given the chairman of that group's permission to use the document, Janssen-Cilag considered that the representative's actions were correct and the company denied a breach of Clause 9.5 of the Code.

Janssen-Cilag stated that in April 2003, the chairman had asked the representative and another company whether the two companies could meet printing costs for 500 copies of the guidelines. They agreed and contributed towards these costs.

Some members of the Interface Prescribing Group expressed a wish to avoid having any company acknowledgement on these documents. The representative in question acceded to these requests. Janssen-Cilag acknowledged that the company's sponsorship of the printing costs should have appeared on the document and thus accepted a breach of Clause 9.9 of the Code.

With regard to Clause 9.1 of the Code, Janssen-Cilag recognized that the complainant felt strongly about the apparent lack of approval of the use of the PCT logo on the guidelines. Given its comments above, Janssen-Cilag urged the Panel to closely examine the question of the ownership of these guidelines and the subsequent appropriate use of relevant NHS logos as 'proof of ownership'. Janssen-Cilag repeated the point that the Interface Prescribing Group included representation from all Birmingham PCTs; the use of any NHS logo should be seen as a matter for the NHS. Janssen-Cilag suggested that the complainant would wish to discuss this matter further with his NHS colleagues and indeed had written a letter to the complainant to this effect. A copy was provided.

Janssen-Cilag stated that it had addressed the comment about declaring sponsorship of the printing costs, which was seen as a benefit for the NHS. The company submitted that once the guidelines had been developed that high standards had been maintained.

Janssen-Cilag stated that the representative had handled his contacts with key members of the Interface Group professionally and with courtesy. The forwarding of the guidelines as an attachment to the letter to another PCT was carried out on the basis of an understanding with the chair of the guidelines development group who had indicated permission for the guidelines to be so discussed. Janssen-Cilag noted that the complainant had written directly to the company to ask it to withdraw all copies from an audit trail. The company repeated that in its view these were NHS copies and issues of withdrawal or circulation were, quite properly, within the domain of the NHS.

Janssen-Cilag stated that apart from the lack of declaration of sponsorship dealt with under Clause 9.9 above, the representative and the company had maintained high standards at all times and therefore it denied a breach of Clause 9.1. Based on its comments above, Janssen-Cilag strongly refuted a breach of Clause 2.

PANEL RULING

The Panel noted that Janssen-Cilag had not been involved in developing the guidelines. Its only role (together with that of another company) was to pay for the printing of the guidelines. This had not been made clear on the document. The Panel considered that the company had in effect failed to clearly indicate its sponsorship of the printing of the guidelines and thus a breach of Clause 9.9 of the Code (2001 edition) was ruled as acknowledged by Janssen-Cilag.

The Panel noted that the guidelines did not state who was responsible for them although a list of members of the Interface Prescribing Group was given. The front cover included the names in logo format of five NHS trusts including the complainant's. One of the Interface Prescribing Group was described as a GP and Primary Care Group Board Member of the complainant's PCT. Janssen-Cilag had also submitted that another person listed as a member of the Interface Prescribing Group was a member of the complainant's PCT.

It appeared that the complainant's PCT might not have seen the guidelines; a letter from the Chief Executive to Janssen-Cilag stated that neither the Professional Executive Committee nor the Board of the PCT had approved the document. In the Panel's view this was a communication problem between those drawing up the guidelines and the PCTs and not Janssen-Cilag's responsibility as the company had no role in developing the guidelines. The chairman of the Interface Prescribing Group had agreed to the guidelines being discussed with other PCTs and they were the subject of an article published in Medicine Matters, May 2003.

The Panel noted that the article published in Medicine Matters was not the same as the document circulated by Janssen-Cilag; in the Panel's view, the published article was substantially different to the guidelines circulated by Janssen-Cilag.

In a letter of 20 August to Janssen-Cilag the chairman of the Interface Prescribing Group stated that the guidelines were in the public domain. There was no reference in the letter to Janssen-Cilag's use of the guidelines. The Chairman's letter to Janssen-Cilag was written some time after the representative's letter to the prescribing adviser which had 13 June stamped on it. In the circumstances the Panel did not consider that Janssen-Cilag had received prior written permission to use the document for promotional purposes. The Panel thus ruled a breach of Clause 9.5 of the Code (2001 edition). The Panel considered that

Janssen-Cilag had failed to maintain a high standard and thus a breach of Clause 9.1 of the Code was ruled. The Panel did not consider that the circumstances warranted a ruling of a breach of Clause 2 which was used as a sign of particular censure and reserved for such use.

Complaint received **8 August 2003**

Case completed **2 October 2003**

CASE AUTH/1505/8/03

PRIMARY CARE TRUST PHARMACIST v DISCOVERY

Sampling of Doxadura

A community care pharmacist from a primary care trust complained about the provision of an unsolicited standard prescription pack of Doxadura (doxazosin) 4mg tablets by Discovery. The pack of 28 tablets had been sent by recorded delivery. The complainant stated that there was no indication that the product was a sample.

The Panel noted that the tablets had not been supplied in response to a written request which had been signed and dated and the pack was not marked 'free medical sample – not for resale' or the like and nor was it accompanied by the summary of product characteristics (SPC). The Panel also noted that no unsolicited medicine must be sent through the post. Breaches of the Code were ruled.

COMPLAINT

A community care pharmacist from a primary care trust (PCT) complained about the provision of an unsolicited prescription only medicine (POM) pack of Doxadura (doxazosin) 4mg tablets by Discovery Pharmaceuticals. The pack of 28 tablets had been sent in a padded envelope by recorded delivery [date stamped 1 August 2003] to the PCT's pharmaceutical adviser at another site and transferred in the internal mail to the complainant; PCT staff were unaware of the contents of the package. As the package was not marked private and confidential, and the addressee was absent, it was opened by another member of the team. Both a pharmacist colleague and the complainant concluded that the package contained what appeared to be a genuine POM pack. A photocopy of the packaging and its contents were provided.

When writing to Discovery to advise it of the complaint the Authority asked it to respond in relation to the requirements of Clauses 17.3, 17.5 and 17.10 of the Code.

RESPONSE

Discovery submitted that it had considered that providing a small number of prescribing advisors with a sample for identification purposes would be useful as it did not promote to GPs by way of a salesforce. Discovery acknowledged that it had not received a written request to do so and so was in breach of Clause 17.3 of the Code.

Discovery stated that whilst the pack itself was not marked 'free medical sample – not for resale' the accompanying letter indicated that the pack had been sent for 'reference purposes'. The company also accepted that it did not include a copy of the summary of product characteristics (SPC) as required by the Code.

Discovery further submitted that it was in breach of Clause 17.10 which stated that 'No unsolicited medicine may be sent through the post'; there had been no prior request.

Discovery stated that the activities complained of arose out of naivety rather than any malicious intent. The company had already amended its marketing policy to ensure that this was not repeated, and would actively endeavour to comply with all aspects of the Code in the future.

PANEL RULING

The Panel noted Discovery's submission that the packs of Doxadura tablets had been sent to prescribing advisors for identification purposes. The supplementary information to Clause 17 of the Code stated that a small sample which was provided only for identification or similar purposes and which was not intended to be used in treatment might be provided to any health professional but was otherwise subject to the requirements of Clause 17.

The Panel noted that the Doxadura tablets had not been supplied in response to a written request which had been signed and dated. A breach of Clause 17.3 was ruled. The pack which was sent was not marked 'free medical sample – not for resale' or the like and nor was it accompanied by the SPC. A breach of Clause 17.5 was ruled. Clause 17.10 stated, *inter alia*, that no unsolicited medicine must be sent through the post. The Panel thus ruled a breach of Clause 17.10. The Panel noted that Discovery had acknowledged all of the above breaches of the Code.

Complaint received **11 August 2003**

Case completed **11 September 2003**

CASE AUTH/1506/8/03

PFIZER v LILLY

Cialis prescribing information

Pfizer complained about the content and presentation of the prescribing information which Lilly had included on promotional material for Cialis (tadalafil). Pfizer supplied Viagra (sildenafil).

With regard to content Pfizer noted that the Cialis summary of product characteristics (SPC) stated that the maximum dosing frequency was once per day but that the daily use of the medication was strongly discouraged because the long-term safety after prolonged daily dosing had not been established. Pfizer noted that the prescribing information stated 'Maximum dosing frequency, once per day' but did not refer to the important key detail that daily dosing was strongly discouraged. Pfizer stated that the SPC actively discouraged daily dosing with Cialis but the prescribing information implied that regular daily dosing was a reasonable thing to do. This clearly misrepresented the SPC and could have safety implications.

The Panel considered that the omission of the SPC statement that daily use was discouraged meant that the prescribing information was not a succinct statement of the dosage information in the SPC. The prescribing information had omitted information which was important to the appropriate use of the product. It was also misleading and inconsistent with the SPC. Breaches of the Code were ruled.

With regard to presentation, Pfizer alleged that in a launch mailing, a formulary pack and a leavepiece, the prescribing information was not clear and legible and overall was difficult to read.

The Panel noted that all three items used narrow print ie lower case letters were generally taller than they were broad; in the Panel's view this did not assist readers. It was a question of overall impression. The Panel decided to consider each item separately.

The Panel considered that on balance the prescribing information in the formulary pack and the launch mailing were sufficiently legible. No breaches of the Code were ruled. The Panel considered that the prescribing information in the leavepiece was not sufficiently legible. The background was darker and the spaces between the lines were less than in the formulary pack and the mailing. The Panel thus ruled a breach of the Code.

Pfizer Limited complained about the promotion of Cialis (tadalafil) by Eli Lilly and Company Limited. The materials at issue were a launch mailing (CI 207), a formulary pack (CI 126) and a leavepiece (CI 167). The launch mailing was no longer in use. The formulary pack was used by representatives and was still in use. The leavepiece was shortly to be withdrawn. Pfizer supplied Viagra (sildenafil).

1 Wording of the prescribing information

COMPLAINT

Pfizer alleged that an important and key detail from the Cialis summary of product characteristics (SPC) did not appear in the Cialis prescribing information and therefore this information was not reflected adequately.

The prescribing information under the section 'Dosage and Administration' stated 'Maximum dosing frequency, once per day'. However, in the Cialis SPC (section 4.2: Posology and method of administration) there was a statement 'Daily use of the medication is strongly discouraged because the long-term safety after prolonged daily dosing has not been established'.

Pfizer stated that the SPC actively discouraged daily dosing with Cialis but the prescribing information implied that regular daily dosing was a reasonable thing to do. This clearly misrepresented the SPC wording and could have safety implications that the prescriber might be unaware of. This was of greatest concern to Pfizer.

Pfizer suggested that a fairer statement relating to this for inclusion in the prescribing information should read 'Daily dosing with Cialis is strongly discouraged'. This was a better option in terms of patient safety for both the patient and the prescriber. The industry had an obligation to ensure patient safety and to consider their well-being.

Pfizer alleged that Lilly was in breach of Clause 3.2 as the prescribing information was inconsistent with the particulars listed in the SPC, Clause 4.2 as the prescribing information was not a succinct statement of the information in the SPC and Clause 7.2 as the prescribing information misled as to the meaning in the SPC. Pfizer noted that the prescribing information would be used by Lilly in other promotional materials.

RESPONSE

Lilly had replied to Pfizer's original complaint stating that it would review the wording of the prescribing information for Cialis in relation to dose regimen. As a result of this review, new prescribing information for Cialis was approved for use from May 2003. A copy was provided which contained the wording 'Daily use of the medication is strongly discouraged'.

In addition to using the new prescribing information for all new material approved for use from mid May onwards, Lilly instituted a plan to review and withdraw or replace materials with the old prescribing information. This process would shortly be completed.

In summary, Lilly had already honoured the undertaking given to Pfizer to review the prescribing information for Cialis and had changed it in a manner which made it consistent with the SPC, as requested by Pfizer. For these reasons none of the points made by Pfizer in relation to the inconsistency of Cialis prescribing information with the Cialis SPC were relevant and Lilly suggested that there was no case to answer on this point.

PANEL RULING

The Panel noted that in the course of inter-company correspondence Lilly had agreed to change the Cialis prescribing information in line with Pfizer's request. Pfizer had subsequently made a complaint under the Code which had to be considered in the usual way. The leavepiece and the formulary pack were still in use with unamended prescribing information.

The Panel noted that the Cialis SPC stated that 'The maximum recommended dosing frequency is once per day' and that 'Daily use of the medication is strongly discouraged because the long-term safety after prolonged daily dosing has not been established'. The prescribing information on the material at issue stated 'Maximum dosing frequency, once per day'.

The Panel considered that the omission of the SPC statement that daily use was discouraged meant that the prescribing information was not a succinct statement of the dosage information in the SPC as set out in Clause 4.2 of the Code. The prescribing information had omitted information which was important to the appropriate use of the product.

Clause 4.1 required that the prescribing information be provided. Clause 4.2 set out the content of the prescribing information. It was not possible to breach Clause 4.2 of the Code. The Panel thus ruled a breach of Clause 4.1 of the Code. The prescribing information was misleading and was inconsistent with the particulars listed in the SPC. The Panel therefore ruled breaches of Clauses 3.2 and 7.2 of the Code.

2 Legibility of prescribing information

COMPLAINT

Pfizer alleged that the prescribing information was not clear and legible in the items at issue and overall was difficult to read.

Pfizer asked Lilly to confirm the font type and size used. Lilly had stated that in its view the font and layout conformed to Clause 4 of the Code based on the size of a lower case 'x'. Lilly had not provided Pfizer with any information relating to the font type used as requested.

Pfizer noted that the supplementary information to Clause 4.1 pointed out that legibility of prescribing information was not simply a matter of type size as Lilly stated in its reply to Pfizer. This was an important point. The prescribing information did not meet many of the recommendations set out in the supplementary information in the Code, ie it had more than 100 characters per line, there was not sufficient spacing to facilitate easy reading, a clear style of type had not been used and clearly emboldened headings had not been used.

Pfizer stated the supplementary information to Clause 4.1 of the Code was not a simple 'check list' of what satisfied legibility of prescribing information. These were important factors, but factors that must be considered alongside the promotional item and the prescribing information as a whole.

The result of this was that the legibility of the prescribing information was poor which discouraged a health professional from reading it; this was of grave concern. Also in view of Pfizer's concerns above regarding an inconsistency with the SPC, the impact of this illegibility was compounded further. A breach of Clause 4.1 of the Code was alleged.

RESPONSE

Lilly provided detailed comments as follows:

Font size and type: The font size of the prescribing information for Cialis on the items at issue was such that the lower case 'x' was 1mm in height as required by the Code. Lilly stated that because print of this size was small it might seem difficult to read. Various characteristics of fonts other than lower case 'x' height contributed to legibility (examples of Bix 2002 and Gaultney 2001 were provided). These included the heights of the ascenders and descenders (neither too short nor too long), the size and shape of the counterforms (adequate white space within the letter shapes was important for legibility in small type), stroke weight (line thickness around 18% of the letter height or width equated with optimum legibility), background colour and contrast (black type on a white, yellow or cream background had maximum legibility), and the presence or absence of serifs (sans serif fonts were recommended for legibility by the Food and Drug Administration).

Based on these published sources, the font used on the items satisfied objective criteria for legibility (enlarged samples were provided). For example, the ratio of the heights of the ascenders and descenders to the 'x' height was the same as for Arial, one of the most widely used sans serif fonts. The counterforms were large, which aided legibility when small point sizes were used, and the stroke width measured from the enlarged samples ranged from 14% to 22% (optimum value for legibility was 18%). The font was a sans serif font which was the type recommended by the FDA on the grounds of legibility, and in all three items the print was black against a white, yellow or cream background which also optimised legibility.

Sufficient spacing to facilitate easy reading: There were two issues here – space between lines and space between words.

Space between lines: Since the proportion of capital letter to lower case letter varied from font to font, Lilly had investigated the relationship between the height of the upper case letters (font height) and the distance between the bottom of the lower case letters on two successive lines (line height) for printed materials from a number of sources. The results were summarised in the following table:

Font height as % line height (ratio)

Font	Cialis API	BMJ	Penguin Paperback	Code Review
Ratio (%)	67%	60%	63%	63%

In addition the line spacing used in each of the 3 items at issue had been compared to the line spacing resulting from use of the default settings in Microsoft Word to print text in Arial, a very widely used sans serif font. This was done by enlarging samples of the

prescribing information for Cialis using a photocopier and then comparing them to text in Arial with the same 'x' height generated using Microsoft Word. In all three cases the line spacing used in the prescribing information for Cialis was slightly more generous than would have been the case if the Arial single spaced font had been used. Thus it was clear that the line spacing of the prescribing information for Cialis was similar to that found in various types of printed material generally accepted as being readable.

Space between words: The space between words in typesetting varied from word pair to word pair both on account of the letters abutting on the space and on account of the nature of the right hand edge of the text (justified or un-justified). Lilly investigated the relationship between the range of distances between words (word space) and the distance between the bottom of the lower case letters on two successive lines (line height) for printed materials from a number of sources. These results were summarised in the following table:

Word space as % line height (ratio)

Word space	Cialis API	BMJ	Penguin Paperback	Code Review
Ratios (%) (max and min)	23%-61%	25%	25%-37%	25%-30%

Thus it was clear that the word spacing of the prescribing information for Cialis was similar to that found in various types of printed material generally accepted as being readable.

Clearly emboldened headings: Inspection of the prescribing information for Cialis on the items showed that emboldened headings were used as well as sub-headings in italics.

Line length: The recommended line length for abbreviated prescribing information was up to 100 characters and spaces per line. Analysis of line length of the abbreviated prescribing information on the items was carried out by converting the text of each item's prescribing information into a non-proportional font (all letters and spaces the same size). This allowed both characters and spaces to be counted easily and an overall impression to be gained. The mean character and space counts per line for each item were different and were summarised in the following table:

Item Code	Item	Mean number of characters and spaces per line
CI 126	Formulary Pack	94.7
CI 167	Leave Piece	99.5
CI 207	Mailing	126.9

Lilly noted that mean values for the formulary pack and leavepiece complied with the line length rule. The mean value for the mailing was 27% greater than recommended by the line length rule. Lilly accepted that item CI 207 might be in breach of the Code on this one technical point. Since the item was a 'one off' mailing, announcing the launch of Cialis, it was no longer in use.

As Pfizer pointed out the supplementary information to Clause 4.1 was not a simple checklist; its purpose was to give recommendations and guidance. Lilly believed that the font, line spacing, word spacing, and emboldening of headings in the prescribing information for Cialis had been prepared in keeping with these recommendations and thus was not in breach of the Code in terms of legibility of the font or text.

PANEL RULING

The Panel noted that the supplementary information to Clause 4.1 of the Code gave recommendations to achieve clarity and assist with legibility.

The Panel dismissed the detailed comments from Lilly regarding the calculations it had made and the enlargements and rearranging that it had undertaken to support its position. The acid test was whether the prescribing information was clear and legible. In that regard the Panel noted that this was a subjective matter, in its view it was not one solved or proved merely by mathematical calculations.

The Panel noted that all three items used narrow print ie lower case letters were generally taller than they were broad; in the Panel's view this did not assist readers. It was a question of overall impression. The Panel decided to consider each item separately.

The Panel considered that on balance the prescribing information in the formulary pack was sufficiently legible. It was printed on a white background with good spacing between the lines to assist legibility. No breach of Clause 4.1 of the Code was ruled in that regard.

The Panel considered that on balance the prescribing information in the launch mailing was sufficiently legible although it was on the limits of acceptability. No breach of Clause 4.1 of the Code was ruled.

The Panel considered that the prescribing information in the leavepiece was not sufficiently legible. The background was darker and the spaces between the lines were less than in the formulary pack and the mailing. The Panel thus ruled a breach of Clause 4.1 of the Code.

Complaint received **11 August 2003**

Case completed **23 September 2003**

CASE AUTH/1509/8/03

PHARMACEUTICAL ADVISOR v GLAXOSMITHKLINE

Notification of Fluarix price increase

A pharmaceutical advisor to a primary care trust (PCT) complained that GlaxoSmithKline had not done all it could to inform PCTs and others that it had increased the price of Fluarix (inactivated influenza vaccine).

In May the Prescription Pricing Authority (PPA) stated that Fluarix cost £3.99. The complainant therefore asked practices to transfer their orders to this product. On ordering GlaxoSmithKline stated that, as of 1 April, the cost of Fluarix had increased to £4.39. The company claimed the price increase was agreed with the Department of Health (DoH). The complainant noted that the July edition of the Monthly Index of Medical Specialities (MIMS) still quoted a price of £3.99. The complainant telephoned the company which insisted that it had told all parties about the price increases and it was not its responsibility to change the prices at the DoH level.

The complainant noted that GlaxoSmithKline's letter about the price increase had not been sent to PCTs at all. The complainant alleged that this was not appropriate when PCTs were the budget holders for these medicines.

The Panel noted that the Fluarix price increase was agreed with the DoH in August 2002 and took effect on 1 April 2003. The Panel noted GlaxoSmithKline's submission that 90% of all Fluarix orders were placed by GP practices. Promotional material stating that the price of Fluarix for the 2003 influenza season would be £4.39 less a 30% discount was sent to GP practices following a representative's request from 6 November 2002 onwards. The prescribing information in the promotional material gave a pre and post 1 April 2003 price.

The Panel did not consider that the failure to notify individual PCTs was unacceptable as alleged. No breach was ruled in that regard.

The Panel noted that GlaxoSmithKline only wrote to MIMS, The Pharmaceutical Journal, the Chemist & Druggist and the PPA on 5 June 2003 notifying them of the price increase. The Panel was concerned that these bodies had not been notified about the price increase until two months after it came into effect and ten months after it had been agreed, particularly given that the price increase had been included in promotional material from 6 November. The PPA and MIMS etc were standard reference sources to which a health professional might turn, at least in the first instance, to obtain up-to-date details of NHS prices. The Panel noted that GlaxoSmithKline had accepted that the delay was an oversight on its part and that procedures had been amended. Nonetheless the Panel considered that high standards had not been maintained and a breach of the Code was ruled.

A pharmaceutical advisor to a primary care trust (PCT) complained about the notification of a price increase of Fluarix (inactivated influenza vaccine) by GlaxoSmithKline UK Ltd.

COMPLAINT

The complainant stated that when looking at cost savings within the PCT prescribing budget she realised that different manufacturers were pricing influenza vaccine at different prices with a varying cost to the prescribing budget of at least 65% from the cheapest to the most expensive.

The complainant received information from the Prescription Pricing Authority (PPA) on 20 May about the prices of the different influenza vaccines; a price of £3.99 was stated for Fluarix. The complainant therefore advised practices that this seemed a reasonably priced option and asked them to transfer their orders to this product. On ordering the product GlaxoSmithKline stated it had increased the price of Fluarix to £4.39 since 1 April 2003. The company claimed this was agreed with the Department of Health (DoH).

The complainant noted that the July edition of the Monthly Index of Medical Specialities (MIMS), which most used to gauge prices, still stated £3.99 as the price for the vaccine. The complainant telephoned the company which insisted that it had sent out communications to this effect to all parties and it was not its responsibility to change the prices at the DoH level.

The complainant provided copies of the May PPA information when the price was still quoted at £3.99. Further MIMS did not record the higher price. The complainant considered that the company had not done all it could to notify the PPA and other bodies (PCTs in particular) of the price increase.

GlaxoSmithKline's letter informing of a price increase had not been sent to PCTs at all. The complainant alleged that this was not appropriate when PCTs were the budget holders for these medicines.

When writing to GlaxoSmithKline the Authority asked it to respond in relation to Clause 9.1 of the Code.

RESPONSE

GlaxoSmithKline explained that the price increase of Fluarix was agreed by the DoH in August 2002 to take effect from 1 April 2003. Promotion of Fluarix to GP practices began in November 2002 for the 2003 influenza season. Promotion of Fluarix was targeted at GP practices rather than any other customer group because almost 90% of Fluarix orders were placed by GP practices. Customers began to place orders for Fluarix from November 2002. The price of Fluarix was increased on 1 April 2003 and applied to all orders placed for the 2003 influenza season (even if customers had ordered Fluarix in November 2002). The national influenza immunisation campaign would begin in September 2003, when customers would take delivery of their Fluarix order.

GlaxoSmithKline stated that it was necessary to agree the price increase of Fluarix with the DoH by August

2002 to alert GP practices in November 2002 to the Fluarix offer (the discount and additional services) that the company would be providing for the 2003 influenza season.

Representatives and the Customer Contact Centre (which took telephone orders for Fluarix) were sent a briefing document on 6 November 2002 notifying them of the increase in the price of Fluarix as of 1 April 2003, a copy of which was provided. Promotional material, consisting of a leavepiece and mailings that were sent to GP practices on the representative's request, was in circulation from 6 November 2002. All of these materials clearly indicated the price of Fluarix for the 2003 influenza season, as follows:

'During the 2003 flu season, Fluarix is available at an NHS list price of £4.39[1] less a 30% discount.

1. The Fluarix NHS list price of £4.39 is effective from the 1st April 2003 and will apply to all orders placed for a delivery during the 2003 flu season.'

Additionally, the prescribing information on all of these materials clearly stated the price of Fluarix before and after 1 April 2003.

Even if a customer had not seen a representative or any of the promotional materials, they would have been aware of the increased price of Fluarix when placing their order with the Customer Contact Centre. In any circumstance, a confirmation letter would also have been sent after the customer had placed the order, detailing the price of Fluarix and any other additional services GlaxoSmithKline had agreed to provide.

It was not usual company practice to send a blanket notification to alert health professionals or the PCTs of a price increase since it would involve sending thousands of letters. Sending such notifications to health professionals would be extremely inappropriate with the number of changes that occurred on an annual basis.

As the majority of orders placed for Fluarix were from GP practices, not PCTs, GlaxoSmithKline therefore did not consider it necessary to specifically alert PCTs to the price increase.

GlaxoSmithKline stated that the letter that was sent to various publications including MIMS, the Pharmaceutical Journal and Chemist & Druggist, notifying them of the price increase of Fluarix was not sent until 5 June 2003. The PPA was also notified on this date. Notifying these publications and the PPA after the price increase had taken effect, was an oversight on the company's part and it had taken the necessary action to ensure this did not happen again.

GlaxoSmithKline noted however, that all manufacturers offered the influenza vaccine at a discount from the NHS list price. Therefore GP practices did not only look in publications like MIMS which simply published the NHS list price, without knowing what discount was being offered from the company. Therefore although certain publications were not notified of the Fluarix price increase in time, in practice purchasers would also contact the company to find out what deal was being offered (including the discounted price of the vaccine). In this case GP practices were being offered a 30% discount on the NHS list price of Fluarix for the 2003 influenza season.

PANEL RULING

The Panel noted that the Fluarix price increase was agreed with the DoH in August 2002 and took effect on 1 April 2003. The Panel noted GlaxoSmithKline's submission that 90% of all Fluarix orders were placed by GP practices. Promotional material indicating the price of Fluarix for the 2003 influenza season at £4.39 less a 30% discount was sent to GP practices following a representative's request from 6 November 2002 onwards. The prescribing information in the promotional material gave a pre 1 April 2003 price and a post 1 April 2003 price. Representatives and the GlaxoSmithKline Customer Contact Centre were notified via a briefing document on 6 November.

The Panel noted GlaxoSmithKline's submission that it was not usual practice to send a blanket notification to alert health professionals or individual PCTs of a price increase. The Panel did not consider that the failure to notify individual PCTs was unacceptable as alleged. No breach of Clause 9.1 was ruled in that regard.

The Panel noted that GlaxoSmithKline only wrote to MIMS, The Pharmaceutical Journal, the Chemist & Druggist and the PPA on 5 June 2003 notifying them of the price increase. The letter provided the new NHS list price and the telephone number for the Customer Contact Centre.

The Panel considered there had been ample time to ensure that the new price for Fluarix was in the public domain as soon as it became effective on 1 April 2003. The Panel was concerned that the PPA and publications such as MIMS had not been notified about the price increase until two months after it came into effect and ten months after it had been agreed, particularly given that the price increase had been included in promotional material from 6 November. The PPA and MIMS etc were standard reference sources to which a health professional might turn, at least in the first instance, to obtain up to date details of NHS prices. The fact that customers might ultimately pay a lower price for a medicine due to discounts offered by the company was irrelevant. The Panel noted that GlaxoSmithKline had accepted that the delay was an oversight on its part and that procedures had been amended to ensure that it did not happen again. Nonetheless the Panel considered that high standards had not been maintained. A breach of Clause 9.1 was ruled

Complaint received **19 August 2003**

Case completed **3 October 2003**

VOLUNTARY ADMISSION BY GLAXOSMITHKLINE

Avandia journal advertisement

GlaxoSmithKline voluntarily advised the Authority that it had breached the Code by publishing an Avandia (rosiglitazone) journal advertisement which promoted the product as monotherapy in the treatment of type 2 diabetes before the company had formally received the relevant marketing authorization. The advertisement had appeared in Pulse, 1 September.

Although GlaxoSmithKline had embargoed the release of all monotherapy materials until approval was duly received, materials had been circulated internally; these materials had not been finally approved. An in-principle approval of the artwork itself was, however, sent to the printers. Unfortunately, as a result of a miscommunication with the printers (for which GlaxoSmithKline took full responsibility), this was interpreted as final approval to publish.

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

While GlaxoSmithKline accepted that the advertisement in question was released prematurely, it asked the Authority to consider whether its publication represented a breach of the Code which stated that a medicine must not be promoted prior to the grant of the marketing authorization. The relevant marketing authorization was officially adopted by the European Medicines Evaluation Agency on 28 August, a fact of which GlaxoSmithKline was aware when the advertisement appeared in Pulse on 1 September.

The Panel noted that the official journal of the European Union stated that the date of the decision with regard to Avandia was 28 August 2003. A European Commission document giving guidance on the decision making procedure stated that the decision took effect from the date of the signature. The Panel concluded that the date of the grant of the marketing authorization for Avandia was 28 August 2003. The advertisement had been published in a journal dated 1 September 2003. The Panel thus ruled no breach of the Code.

COMPLAINT

GlaxoSmithKline UK Ltd voluntarily advised the Authority that it had inadvertently breached Clauses 3.1 and 3.2 of the Code by prematurely publishing an Avandia (rosiglitazone) advertisement (ref AVD/DPS/03/09348/1) which promoted the product as monotherapy in the treatment of type 2 diabetes. The advertisement had appeared in Pulse, 1 September.

An application for the use of Avandia as monotherapy was submitted to the European Medicines Evaluation Agency (EMEA) and a positive opinion was given in May; the adoption date was 28 August. The licence was formally received on 2 September.

GlaxoSmithKline had embargoed the release of all monotherapy materials until this approval was duly received. Materials had, however, been prepared in anticipation of the extended licence, and circulated internally. Up to the time of writing, these materials had not been given final approval by the requisite medical and marketing signatories. An in-principle approval of the artwork itself was, however, sent to the printers. Unfortunately, as a result of a miscommunication between GlaxoSmithKline and the printers (for which GlaxoSmithKline took full responsibility), this was interpreted as final approval to release advertisements to journals.

Through a routine enquiry to its medical information department, GlaxoSmithKline was made aware on the afternoon of 1 September that an Avandia monotherapy advertisement had appeared that day in Pulse. GlaxoSmithKline immediately took steps to ensure that any additional publication of such material was halted, and the embargo with its agencies reinforced. The advertisement in Pulse was the only one to appear in print.

GlaxoSmithKline notified the Authority and the advertising division of the Medicines and Healthcare products Regulatory Agency on 1 September that it had become aware of this error. An urgent internal audit was currently in progress to ascertain exactly how the misunderstanding in question arose.

GlaxoSmithKline regretted this unfortunate event and all necessary steps would be taken to ensure that such an oversight did not recur.

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

The Authority requested that GlaxoSmithKline respond in relation to the provisions of Clause 3.1 of the Code.

RESPONSE

GlaxoSmithKline stated that it had little substantive to add to the letter already sent to the Authority, except to confirm that steps were actively being taken to review and reinforce the current process for the formal release of advertisement copy to journals from agencies.

While GlaxoSmithKline fully accepted that the advertisement in question was released prematurely, it asked the Authority to consider whether its publication did, in fact, represent a breach of Clause 3.1 of the Code which stated 'A medicine must not be promoted prior to the grant of the marketing authorization which permits its sale or supply'. The

relevant marketing authorization was officially adopted by the EMEA on 28 August, a fact of which GlaxoSmithKline was aware when the advertisement appeared in Pulse on 1 September. The prescribing information on the advertisement was in full accordance with the final summary of product characteristics.

This was not to say that GlaxoSmithKline viewed this incident as anything other than a serious failure of its normal procedures; simply that on reflection it was unsure as to whether it could be construed as a formal breach of the Code.

PANEL RULING

The Panel noted that the official journal of the European Union stated that the date of the decision with regard to Avandia was 28 August 2003. A European Commission document giving guidance on the decision making procedure stated that the decision took effect from the date of the signature.

The Panel concluded that the date of the grant of the marketing authorization for Avandia was 28 August 2003. The advertisement had been published in a journal dated 1 September 2003. The Panel thus ruled no breach of Clause 3.1 of the Code.

During its consideration of this case the Panel was very concerned that material which had not been certified by GlaxoSmithKline as required by Clause 14 of the Code had been published. The company was reviewing its procedures to ensure that such an oversight did not recur. The Panel requested that GlaxoSmithKline be advised of its views.

Proceedings commenced **5 September 2003**

Case completed **30 September 2003**

CASE AUTH/1514/9/03

AVENTIS PASTEUR MSD v GLAXOSMITHKLINE

Promotion of Havrix

Aventis Pasteur MSD complained about a folder for Havrix (hepatitis A vaccine) which was mailed to GP surgeries by GlaxoSmithKline. The claim was made that the seropositivity rates 2 weeks after first dose, as shown across a range of clinical studies in adults, was 87-96% for Havrix and 78-96% for Avaxim (Aventis Pasteur MSD's product). Aventis Pasteur MSD noted that the data was presented in such a way as to ensure that readers made a direct comparison between the two. However, the results came from different studies and involved dissimilar groups and methodologies. In the only fair and valid comparison of the immunogenicity of Avaxim and Havrix, a head-to-head study, the results favoured Avaxim (Zuckerman *et al* 1997). Aventis Pasteur MSD alleged that the presentation of the data was not balanced, fair, objective or unambiguous.

The Panel noted that the results stated in the folder for Avaxim were taken from five studies. Only one small study (n=41) had reported a rate of 78.1%. The other four larger studies (n ≥ 210) gave seroconversion rates of 93.4-95.7%. It thus appeared that a rate of 78.1% might be a rogue result.

With regard to Havrix, the Panel noted that Briem and Safary (1994) had studied its immunogenicity in adults of different ages. The results showed that in patients aged 40-62 years (n=66) the seroconversion rate was 77% at 15 days compared to 90% in patients aged 20-39 (n=134). There was no seroconversion rate reported for the overall population. Although 77% was with regard to a specific population the Panel queried whether the lower figure of 87% given for Havrix in the material at issue was correct. Overall the Panel considered that the data and its presentation was misleading and an unfair comparison. Breaches of the Code were ruled.

The claim 'Havrix provides protection for the whole family (over 12 months of age) …' was followed by the logo for Havrix Monodose. Havrix Monodose, however, was licensed for use in persons aged 16 years and over; Havrix Junior Monodose was for children. In Aventis Pasteur MSD's view the presentation of the claim and the product logo was a potential safety issue as it might lead to readers giving Havrix Monodose (as opposed to Havrix Junior Monodose) to a child. Aventis Pasteur MSD alleged that the claim was not in accordance with the marketing authorization for Havrix Monodose.

The Panel considered that the presentation of the logo and the claim was misleading and inconsistent with the summary of product characteristics. A breach of the Code was ruled.

Aventis Pasteur MSD Ltd complained about the promotion of Havrix (hepatitis A vaccine) by GlaxoSmithKline UK Ltd. The material at issue was a folder which included promotional material for Havrix as well as information sheets to be given by the health professional to the patient following vaccination against hepatitis A (Ref HVX/MLP/03/07948/1 April 03). The item was mailed to GP surgeries in June 2003.

1 Section headed 'Well trusted'

Part of this section included a comparison of Havrix with Aventis Pasteur MSD's product Avaxim. The statement 'Seropositivity rates for anti-HAV 2 weeks after first dose as shown across a range of clinical studies in adults' appeared in a box above a line of

four boxes, two yellow and two blue. The yellow boxes stated 'Havrix' and '87-96%'. The blue boxes stated 'Avaxim' and '78-96%'. Six studies were cited in support of the claims.

COMPLAINT

Aventis Pasteur MSD stated that the presentation of the data, side by side, ensured that readers made a comparison between the two. However, comparisons of the results of clinical studies carried out on dissimilar groups and/or using dissimilar methodologies were fraught with difficulties and likely to be invalid and misleading. GlaxoSmithKline had agreed with this view in a letter to Aventis Pasteur MSD.

The studies in question were carried out on groups with widely varying demographic characteristics and the measurement of antibody responses was carried out using ELISA assays in some studies and modified radio-immuno assays in others. In addition, GlaxoSmithKline failed to make it clear that the only fair and valid comparison of the immunogenicity of Avaxim and Havrix, in a head-to-head study, favoured Avaxim (Zuckerman *et al* 1997).

The key features of the six studies cited by GlaxoSmithKline were summarised by Aventis Pasteur MSD in a table.

GlaxoSmithKline claimed that it had presented the full range of available clinical data in a fair and balanced way. Aventis Pasteur MSD disagreed as GlaxoSmithKline had attached no significance and given no prominence to the only true comparative head-to-head data available, which, because of its design, stood out from the remainder of the studies referenced. Further, GlaxoSmithKline had presented the data and used graphics in a way which deliberately encouraged a comparison of data which were not scientifically comparable.

Aventis Pasteur MSD alleged that the presentation of the data was not balanced, fair, objective or unambiguous in breach of Clauses 7.2 and 7.3 of the Code.

RESPONSE

GlaxoSmithKline stated that the seropositivity rates were shown under a heading that clearly stated 'across a range of clinical studies in adults' and all of the studies had been referenced. The ranges had been shown to illustrate the balance of evidence, as the results from different studies varied according to methodology as Aventis Pasteur MSD had noted. There was no attempt to mislead by suggesting that direct comparisons could be drawn between the results of individual studies and GlaxoSmithKline did not accept that this constituted a breach of the Code.

PANEL RULING

The Panel noted that Zuckerman *et al* was the only study that directly compared the seroconversion rates for Avaxim (95.7%) and Havrix (87.1%). The other studies cited by GlaxoSmithKline were not comparative studies and thus established seroconversion rates for only one or other of the products.

The Panel noted that the range for Avaxim was given as 78.1%-95.5%. The data was taken from five studies. Only one of the studies had reported a rate of 78.1% and this was in a small population of 41. The four other studies were on much larger populations (of at least 210 participants) and gave seroconversion rates of 93.4-95.7%. It thus appeared that a rate of 78.1% might be a rogue result.

With regard to Havrix the Panel noted that the seroconversion rate ranged from 77%-96% according to Aventis Pasteur MSD's review of the six studies cited by GlaxoSmithKline, although the material at issue stated that it was 87%-96%. The figure of 77% cited by Aventis Pasteur MSD was from Briem and Safary (1994) who had studied the immunogenicity of Havrix in adults of different ages. The results showed that in patients aged between 40 and 62 years (n=66) the seroconversion rate was 77% at 15 days compared to 90% in patients aged between 20 and 39 years (n=134). There was no seroconversion rate reported for the patient population overall. The Panel noted that the figure of 77% was with regard to a specific patient population but nonetheless queried whether the lower figure of 87% given in the material at issue was correct.

The Panel considered it was unfair to present the comparison as if the results could be directly compared. The ranges were from different studies. The one direct comparison had not been presented as such.

Overall the Panel considered that the data and its presentation was misleading and an unfair comparison. The Panel ruled breaches of Clauses 7.2 and 7.3 of the Code.

2 Section headed 'Well travelled'

The heading was followed by a claim that 'Havrix provides protection for the whole family (over 12 months of age) and is approved in over 100 countries world-wide' and the logo for Havrix Monodose.

COMPLAINT

Aventis Pasteur MSD noted that Havrix Monodose was licensed for use in persons 16 years and over. The juxtaposition of the claim and the logo might lead individuals to believe that Havrix Monodose could be used in individuals from 12 months of age. GlaxoSmithKline asserted that 'Havrix Monodose' applied to both products: Havrix Monodose and Havrix Junior Monodose. Aventis Pasteur MSD disagreed. In its view this was a potential safety issue, which might lead to readers giving Havrix Monodose (as opposed to Havrix Junior Monodose) to a child. Aventis Pasteur MSD alleged that the claim was not in accordance with the marketing authorization for Havrix Monodose in breach of Clause 3.2 of the Code.

RESPONSE

GlaxoSmithKline submitted that the claim clearly mentioned only Havrix and as such was intended to refer to both adult and junior formulations of the vaccine.

The Havrix Monodose logo when used alone could refer to both adult and junior formulations of the product (ie both Havrix Monodose and Havrix Junior Monodose). Furthermore the accompanying prescribing information quite clearly covered both the adult and junior formulations.

GlaxoSmithKline disagreed that this constituted a safety issue and did not consider it to be in breach of the Code.

PANEL RULING

The Panel considered that the presentation of the Havrix Monodose logo beneath the claim that 'Havrix provides protection for the whole family (over 12 months of age) …' was misleading as it implied that Havrix Monodose could be used in children and that was not so. Havrix Junior Monodose was licensed for children. The Panel considered that the section was inconsistent with the summary of product characteristics and ruled a breach of Clause 3.2 of the Code.

Complaint received **9 September 2003**

Case completed **7 October 2003**

CODE OF PRACTICE REVIEW – NOVEMBER 2003

Cases in which a breach of the Code was ruled are indexed in **bold type**.

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1476/6/03	**Procter & Gamble v Lagap**	**Ipocol journal advertisement**	**Breaches Clauses 7.2 and 7.4**	**No appeal**	**Page 70**
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1498/7/03	Pharmaceutical Company Employee v GlaxoSmithKline	Requip journal advertisement	No breach	No appeal	Page 87
1499/7/03	**Lagap v Procter & Gamble**	**Promotion of Asacol**	**Two breaches Clause 7.2**	**No appeal**	**Page 88**
1500/7/03	**Crookes Healthcare v Sankyo Pharma**	**Cetraben journal advertisements**	**Breaches Clauses 7.9, 7.10 and 8.1**	**No appeal**	**Page 94**
1501/8/03	**Bristol-Myers Squibb and Sanofi-Synthelabo v Sankyo Pharma**	**Olmetec leavepiece**	**Breaches Clauses 7.2 and 7.3**	**No appeal**	**Page 97**
1502/8/03	**Novo Nordisk v Orion Pharma**	**Promotion of Indivina**	**Two breaches Clause 7.2 Two breaches Clause 7.4**	**No appeal**	**Page 98**
1503/8/03	**General Practitioner v Leo Pharma**	**Sponsored journal**	**Breaches Clauses 4.8, 7.2, 9.1, 9.10 and 10.1**	**No appeal**	**Page 100**
1504/8/03	**Primary Care Trust Chief Executive v Janssen-Cilag**	**Atypical Anti Psychotic Shared Care Guidelines**	**Breaches Clauses 9.1, 9.5 and 9.9 (all 2001 edition)**	**No appeal**	**Page 104**
1505/8/03	**Primary Care Trust Pharmacist v Discovery**	**Sampling of Doxadura**	**Breaches Clauses 17.3, 17.5 and 17.10**	**No appeal**	**Page 106**
1506/8/03	**Pfizer v Lilly**	**Cialis prescribing information**	**Breach Clause 3.2 Two breaches Clause 4.1 Breach Clause 7.2**	**No appeal**	**Page 107**
1509/8/03	**Pharmaceutical Advisor v GlaxoSmithKline**	**Notification of Fluarix price increase**	**Breach Clause 9.1**	**No appeal**	**Page 110**
1513/9/03	Voluntary admission by GlaxoSmithKline	Avandia journal advertisement	No breach	No appeal	Page 112
1514/9/03	**Aventis Pasteur MSD v GlaxoSmithKline**	**Promotion of Havrix**	**Breaches Clauses 3.2, 7.2 and 7.3**	**No appeal**	**Page 113**

PRESCRIPTION MEDICINES CODE OF PRACTICE AUTHORITY

The Prescription Medicines Code of Practice Authority was established by The Association of the British Pharmaceutical Industry (ABPI) in 1993 to operate the Code of Practice for the Pharmaceutical Industry at arm's length from the ABPI itself.

Compliance with the Code is obligatory for ABPI member companies and, in addition, about seventy non member companies have voluntarily agreed to comply with the Code and to accept the jurisdiction of the Authority.

The Code covers the advertising of medicines to health professionals and administrative staff and also covers information about such medicines made available to the general public.

It covers:

- journal and direct mail advertising
- the activities of representatives, including detail aids and other printed material used by representatives
- the supply of samples
- the provision of inducements to prescribe, supply, administer, recommend or buy medicines by the gift, offer or promise of any benefit or bonus, whether in money or in kind
- the provision of hospitality
- the organisation of promotional meetings
- the sponsorship of scientific and other meetings, including payment of travelling and accommodation expenses
- the provision of information to the general public either directly or indirectly, including by means of the Internet
- all other sales promotion in whatever form, such as participation in exhibitions, the use of audio-cassettes, films, records, tapes, video recordings, electronic media, interactive data systems, the Internet and the like.

Complaints submitted under the Code are considered by the Code of Practice Panel which consists of the three members of the Code of Practice Authority acting with the assistance of independent expert advisers where appropriate. Both complainants and respondents may appeal to the Code of Practice Appeal Board against rulings made by the Panel. The Code of Practice Appeal Board is chaired by an independent legally qualified Chairman, Mr Nicholas Browne QC, and includes independent members from outside the industry.

In each case where a breach of the Code is ruled, the company concerned must give an undertaking that the practice in question has ceased forthwith and that all possible steps have been taken to avoid a similar breach in the future. An undertaking must be accompanied by details of the action taken to implement the ruling. Additional sanctions are imposed in serious cases.

Complaints about the promotion of medicines should be sent to the Director of the Prescription Medicines Code of Practice Authority, 12 Whitehall, London SW1A 2DY (telephone 020 7930 9677 facsimile 020 7930 4554).