PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

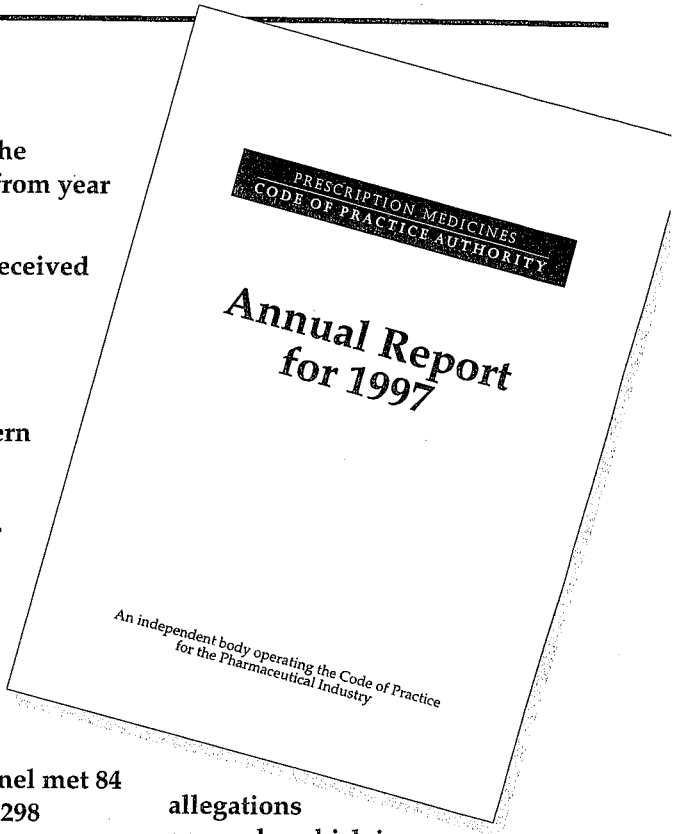
NUMBER 21 AUGUST 1998

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

Annual Report for 1997

The Annual Report of the Prescription Medicines Code of Practice Authority for 1997 has now been published. As previously reported in the Review, there were 145 complaints in 1997 as compared with 104 in 1995 and 102 in 1996. The average number of complaints in the five years since the establishment of the Authority has been just under 118 per year. In 1997 the number of cases which the Authority had to deal with was 165, the highest ever. In 1994 when the number of complaints was also 145, the number of cases was 159. There are usually more cases than complaints because some complaints involve allegations against more than one company. There is no apparent reason for the wide variations in the number of complaints from year to year.

Of the 145 complaints received in 1997, 48 came from companies and 79 from members of the health professions. This was a return to the usual pattern in that most complaints came from the health professions. In 1996, for the first and so far the only time, the number of complaints from companies exceeded the number from the health professions.



The Code of Practice Panel met 84 times in 1997 and made 298 rulings. More than one ruling is needed in a case when multiple allegations are made, which is particularly the case with inter-company complaints. Of these 298 rulings, 252 (85%) were accepted by the parties, 30 (10%) were unsuccessfully appealed to the Code of Practice Appeal Board and 16 (5%) were successfully appealed. The Appeal Board, under the Chairmanship of Mr Philip Cox QC, met 8 times in 1997.

Copies of the Authority's Annual Report for 1997 are available free of charge from the Authority.

IFPMA Meeting on the Internet and pharmaceuticals

The International Federation of Pharmaceutical Manufacturers Association (IFPMA) is to hold a symposium on "The Internet and Pharmaceutical Products: The State of the Art and the Way Forward" on Tuesday, 6 October 1998, in Geneva.

The preliminary programme and registration forms can be obtained from IFPMA at 30 rue de St-Jean, PO Box 9, 1211 Geneva 18, Switzerland,
Telephone 00 41 22 340 1200,
Facsimile 00 41 22 340 1380.
Email: admin@ifpma.org

The symposium will focus on issues relating to the quality and authenticity of pharmaceutical information on the Internet and the misuse of the Internet to facilitate cross-border trade in pharmaceuticals outside normal distribution channels. These were the two main issues arising out of a World Health Assembly Resolution on "Cross-border advertising, promotion and sale of medicinal products using the Internet".

The IFPMA has recently established a Task Force on the Internet and Pharmaceuticals of which Heather Simmonds, the Director of the Authority, is a member.

The Task Force will be helping to prepare an IFPMA position paper and guidance for companies about the Internet.

BE BOLD

Companies are reminded that in promotional material, including abbreviated advertisements, the non-proprietary name or names must appear adjacent to the most prominent display of the brand name in not less than 10 point bold (or in a type size which occupies a total area not less than that taken by the brand name).

Although the non-proprietary name usually does appear in the correct position, it is frequently not in 10 point bold and companies are requested to check their materials to ensure compliance in this regard.

CODE OF PRACTICE TRAINING

Training seminars on the Code of Practice, open to all comers, are run by the Code of Practice Authority on a regular basis at the Royal Society of Medicine in London.

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

The next Code of Practice seminar for which places remain available takes place on Thursday, 10 December 1998.

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 Vicki Meyrick for details (0171-930 9677 extn 1443).

How to contact the Authority

Our address is:

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

Telephone: 0171-930 9677
Facsimile: 0171-930 4554

Copies of the Code of Practice for the Pharmaceutical Industry and of this Review can be obtained from Vicki Meyrick (0171-930 9677 extn 1443).

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

Heather Simmonds: 0171-747 1438
Etta Logan: 0171-747 1405
Jane Landles: 0171-747 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.

CASES AUTH/629/10/97 AND AUTH/642/11/97

CONSULTANT NEONATOLOGIST AND SERONO v BRITANNIA

Promotion of Alec

A consultant neonatologist and Serono complained separately about the promotion of Alec by Britannia. Alec (pumactant) was a synthetic surfactant while Serono marketed Curosurf (poractant alfa), a natural surfactant. Six promotional items were at issue.

The title of a mailer "Survival - The most important outcome" was alleged to be inappropriate as survival without associated morbidity was the primary aim. Survival alone was not always difficult to achieve. The Panel considered that the mailer could have been given a more sympathetic title in this very sensitive area of medicine but did not consider that the Code had been breached and ruled accordingly. Across two pages was the header "Alec reduced neonatal mortality by 48%". The Panel considered that the layout of one of the pages would invite readers to make comparisons between the various surfactant groups and favourably compare Alec with the rest, but Alec had not been directly compared with any of the other surfactants. The Panel considered that the data presented was misleading and confusing and it was ruled in breach. The description in both a table of results and a bar chart "All animal derived surfactants as prophylactic treatment" was ruled to be misleading and in breach of the Code as it would be taken by most readers to mean that all animal derived surfactants were included but this was not the case as poractant alfa (Curosurf) was not included due to a lack of data. The claim "Alec reduces mortality at least as well as other surfactants when given at birth" was ruled in breach as it implied that Alec had been compared with all other surfactants, which was not so. The claim had not been substantiated.

A table of results was headed "The recently published Cochrane Collaboration meta-analysis comparing synthetic and animal derived surfactant showed no significant difference in mortality". The Panel considered that the mailer had not accurately reflected the conclusions of the Cochrane report and ruled a breach. The author of the Cochrane report favoured natural surfactants over synthetic agents but the data had been presented in the mailer in support of a claim of equivalence. A claim referring to Alec as "... being the most frequently used surfactant in the UK" was ruled in breach as a superlative could only be used in respect of statements of fact that could be very clearly demonstrated. The situation as to evidence of sales and usage of surfactants was not simple and a superlative was inappropriate. The claim "reduced parenchymal brain haemorrhages by 33%" was considered to be misleading and ruled in breach. Although the claim accurately reflected the findings in a cited study, the clinical importance of those findings would not be apparent to the reader.

The claim "improved compliance by 50% within 6 hours" was considered to be misleading and ruled in breach. The Panel did not consider that the claim was misleading because of the trial design, as alleged, and no breach was ruled in that regard, but the main thrust of the mailer in question had been to compare Alec with other surfactants and there was no statement that the respiratory compliance results were achieved versus placebo. A number of allegations were made that Alec was being promoted outside of the terms of its licence because the prescribing information clearly stated "... gestational age 25 to 29 weeks" while studies used to substantiate claims included lower gestational ages. The Panel did not consider that there had been promotion outside the licence and ruled accordingly. One claim, however, which specifically mentioned "... babies of 23 to 30 weeks' gestation ..." was ruled to be misleading. A number of claims such as "reduced neonatal mortality", "reduced incidence and severity of RDS" and "improved compliance by 50%" were alleged to be hanging comparisons and in breach because comparators were not given. The Panel considered that it was arguable whether these claims were strictly "hanging comparisons" but, given that the main thrust of the mailer in question was to compare Alec with other surfactants, it was misleading not to state that the comparator was placebo and a breach was ruled. A breach was ruled because of the failure in items which were of more than four pages to state where the prescribing information could be found.

The claim "The two phospholipids in Alec, dipalmitoylphosphatidylcholine (DPPC) and unsaturated phosphatidylglycerol (PG), are a simple replacement for the two phospholipids which are deficient in the lungs of premature babies" was considered to be misleading and in breach because it was an oversimplification of what was a complicated area of medicine. Some readers might assume from the claim that Alec simply restored babies' lungs to normal by replacing what was missing. This was not so, the situation was much more complex. The claim "The clinical trials undertaken with Alec reflect clinical practice. The only exclusion was lethal congenital malformations. This means that the results can be applied directly to the effect of Alec when used in clinical practice" was considered by the Panel to overstate the position and be misleading given the reservations expressed by the authors in the referenced clinical papers. A breach of the Code was ruled.

A mailer gave mortality results from a trial and in a separate paragraph mortality results from another trial, each paragraph being referenced to a different trial. The Panel considered that readers would be misled into assuming that they were two separate trials, the results of one confirming the results of the other. This was not so as the babies in one of the trials subsequently formed part of the other. The presentation was misleading and the Panel ruled a breach. A claim that "Animal derived surfactants have not been shown to reduce the incidence of serious brain damage" was referenced to two papers. The Panel considered that the two trials were so different that their results with regard to brain haemorrhages could not be compared. The way the data on brain haemorrhage was presented was misleading and gave undue weight to the limited positive data for Alec. A breach of the Code was ruled.

No breach of the Code was ruled in relation to a claim that in babies of less than 30 weeks gestation Alec

improved compliance by 50% within 6 hours. The Panel considered that the reference given supported the claim. The claim "Alec has the smallest volume of any surfactant at 1.2ml per dose" was ruled in breach because for very small babies Alec did not have the smallest volume of any surfactant. In relation to the claim "Cardiorespiratory status maintained during administration", the Panel considered that it was supported by the cited reference but although the mean age of the babies studied had been 28 weeks' gestation, babies of up to 37 weeks' gestation had been included in the trial. Alec was only for use in babies of 25-29 weeks' gestation. The Panel considered that the claim had been based on a population which included older, more stable, babies than those for which Alec was indicated. The Panel considered it to be misleading and it was ruled in breach.

The claim "Alec treated babies had improved their respiratory compliance by 50% within 6 hours" appeared above a graph depicting changes in respiratory compliance with time after Alec administration. The claim ".... by 6 hours a baby treated at birth with Alec will have a 50% increase in tidal volume for the same ventilation pressure" appeared below the graph. Results with Alec were then compared with results from two other studies in which babies had been treated with animal derived surfactants. The Panel considered that the layout would lead most readers to assume that the statement regarding a 50% increase in tidal volume was a direct extrapolation of an improved respiratory compliance of 50%. Although respiratory compliance and tidal volume were connected they were not interchangable. The statement about tidal volume was misleading and the Panel ruled it in breach. Below the two claims and the graph was a statement regarding changes in respiratory compliance observed with animal derived surfactants". The statement began "This effect on respiratory compliance compares with ..." thus inviting readers to directly compare results with Alec and results observed with animal derived surfactants. There had been no direct comparisons of Alec with animal derived surfactants. The implied comparison was thus misleading and the Panel ruled it in breach. No breach was ruled in relation to the labelling of the graph as the Panel considered that it would be obvious that the claim regarding improved respiratory compliance was in comparison to control. The claim "Alec treatment has a gentle onset of action and does not destabilise the baby" was considered by the Panel to have been substantiated by the reference cited and no breach was ruled.

A number of statements regarding animal derived surfactants were referenced to eleven separate papers. The page in question ended with a general comparison of animal derived surfactants with Alec stating "The rapid change in oxygenation seen in some babies after treatment with animal derived surfactants may cause problems and confers no extra benefits over the gentle onset of action of Alec". The Panel considered that this statement was vague. Alec had never been compared directly to any other surfactant and the Panel considered that the comparison of animal derived surfactants with Alec was not supported by clinical data. Overall the Panel considered this section to be unclear and inadequately supported by the data and therefore misleading. A breach of the Code was ruled.

A cost comparison compared the costs of colfosceril palmitate, poractant alfa, beractant and Alec, giving cost of single dose vials, "recommended dose range" and "treatment cost range". The Panel considered that it was misleading to give the cost of that part of the vial which would be used. The whole vial had to be paid for even if only a part of it was used. The Panel considered that this, and the failure to state the basis on which the costs had been calculated, was misleading and a breach of the Code was ruled. No breach was ruled in relation to criticism of the use of basic NHS prices rather than contract prices.

The claim "This simple formulation avoids sensitisation of the lungs" was ruled in breach. It was too strong given the evidence. In the Panel's view, the difference was that with natural surfactants there was a possibility of sensitisation whereas with Alec that was unlikely. The claim "Administration of Alec is associated with minimal disturbance to the baby" was considered by the Panel to be misleading and was ruled in breach. The cited paper had included babies of a gestational age of 25-37 weeks (median 28). The age of the babies at administration of Alec had been 21-43 hours (median 26). The Panel considered that the claim had not been put into context with respect to the gestational age of the babies and their age in hours. Some readers would assume that the babies had been less than 30 weeks' gestation and that the effect being reported was after the first dose of Alec, administered soon after birth, which was not so.

A consultant neonatologist (Case AUTH/629/10/97) and Serono Laboratories (UK) Limited (Case AUTH/642/11/97) complained separately about the promotion of Alec by Britannia Pharmaceuticals Limited. Alec (pumactant) was a synthetic surfactant while Serono marketed Curosurf (poractant alfa) a natural, or animal derived, surfactant.

There were six promotional items at issue.

A Mailer entitled "Survival - The most important outcome" (AL.ML-SUR.VI)

This was a four page mailer which had two flaps, one of which was a detachable reply paid card while the other was essentially an extension of pages 3 and 4 and had been used to list the 28 references cited in the piece. Britannia did not state to whom the mailer had been sent but Serono stated that it had been available on an exhibition stand.

1 Title "Survival - The most important outcome"

Case AUTH/629/10/97

COMPLAINT

The consultant neonatologist alleged that the title was thoroughly inappropriate. Preterm birth was a traumatic experience for carers and parents alike and everyone strove to provide appropriate counselling and care for very low birthweight babies. To suggest that survival was the primary aim of that care was misleading and irresponsible. The complainant considered that if Britannia had taken the trouble to ask parents of children with handicaps resulting from survival of preterm delivery whether this was true it would get a very mixed response. The primary aim in delivering neonatal intensive care was survival without associated morbidity - a normal long-term outcome. Survival alone was not always difficult to achieve. It was avoiding brain damage and long term lung problems that presented the greatest challenge. Infants could remain oxygen dependent for several years with further consequences affecting them

throughout their lives. Survival was certainly not the all-important outcome.

RESPONSE

Britannia was sorry that the phrase "Survival - The most important outcome" had apparently caused offence; this was not intended. The purpose was simply to suggest in a simple phrase that survival was more important than other outcomes such as the difference in oxygen in the first few hours, the incidence of pneumothoraces, patent ductus arteriosus and even brain haemorrhages. The first thing parents and professionals wanted was that a very premature baby survived. Without that, any improvement brought about by a treatment was useless. The next objective was that the infant survived to be healthy. The purpose of this leaflet was simply to provide information about survival.

Case AUTH/642/11/97

COMPLAINT

Serono alleged that the title of the mailer, "Survival - The most important outcome", was an insult, as morbidity was considered by clinicians, nursing staff and parents to be equally important. Bronchopulmonary dysplasia (BPD) *per se* was disabling; however most infants showed slow improvement and eventually recovered sufficiently to survive without mechanical ventilation and supplementary oxygen; however this was not without long-term pulmonary sequalae. That BPD was as important an outcome was borne out by many workers who expressed their results in terms of a favourable outcome being survival without bronchopulmonary dysplasia or other concurrent diagnosis.

RESPONSE

Britannia noted that Serono had expressed the view that outcomes other than mortality were considered important by many although there was no specific allegation of a breach of the Code. Whilst Serono's view and statements were not disputed, Britannia contended that the slightly provocative title of the mailer did not breach any clauses of the Code.

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel noted that the front page of the mailer contained only the hot air balloon marque of Alec and the title "Survival - The most important outcome". There was no direct reference to respiratory distress syndrome. The Panel noted that Alec was licenced to reduce neonatal mortality in premature babies who were at risk of developing, or who had developed, respiratory distress syndrome. Alec was not licenced to reduce morbidity. The Panel noted the complainants' concerns and accepted that survival alone was not the most important outcome. In the Panel's view, Alec was indicated in a very sensitive area of medicine and the mailer could have been given a more sympathetic title. As it stood, however, the Panel did not consider that the title was in breach of Clause 9.1 of the Code and ruled accordingly.

2 Misrepresentation of the current medical literature

Pages 2 and 3 of the mailer gave a meta-analysis of the results of twenty four clinical papers detailing the reduced neonatal mortality associated with synthetic and natural surfactants as either rescue treatment or prophylaxis. The results were given in various formats. Running across the two pages was the header "Alec reduced neonatal mortality by 48%".

a) Reduction in neonatal mortality

On page 2 of the mailer were various statements and figures regarding the reduced neonatal mortality seen with Alec and with other surfactants. A table of results gave the mortality in controls and the mortality in treated for "all animal derived surfactants" used as rescue treatment and as prophylactic treatment, colfosceril palmitate used as rescue treatment and as prophylactic treatment and for Alec as prophylactic treatment. The figures given for Alec were 30% mortality in the control group and 19% mortality in the treated group. At the bottom of the page was a bar chart entitled "Increased neonatal unit survival for every 100 babies treated with surfactant". The bars depicted the number of babies saved for every 100 treated with various surfactants, either as prophylactic treatment or as rescue treatment. The number of babies saved with Alec as prophylactic treatment was given as 11, more than with any other surfactant.

Case AUTH/629/10/97

COMPLAINT

The complainant noted that the mailer compared published mortality rates between surfactants. It suggested that mortality with Alec was lower than with other surfactants. This was grossly misleading. The complainant had used Alec and frequently collected babies that had had Alec from referring units and this was certainly not the complainant's experience. The consultant noted that the mortality quoted in the table was actually death on the neonatal unit. This was a different interval from many of the other figures quoted.

The complainant stated that the bar chart on page 2 was totally without basis in statistical science. It appeared to be a direct subtraction of mortality in treated infants from mortality in controls, taken from the table above it. This comparison would only be true if the mortality in the control group was constant. This, of course, would be impossible as all of these trials would have had differing inclusion and exclusion criteria, not to mention that they were done at various stages in "history" when mortality rates were quite different to today. Additionally, the gestational age range of babies treated differed in the groups.

RESPONSE

Britannia submitted that there was no claim, as suggested

by the complainant, that mortality was lower than with other surfactants. The data presented supported the statement "Alec reduces mortality at least as well as other surfactants ...". The text above the table on page 2 stated that the table compared the effects of various surfactants on "reported mortality", not "death on the neonatal unit" as suggested. Britannia submitted that the mortality data presented here correctly reflected the published trials and was not misleading.

With regard to the graph at the bottom of page 2, Britannia submitted that whilst there was no perfect way of comparing mortality rates in the various (inevitably different) published clinical trials, the method of graphical comparison which had been adopted was no more potentially "misleading" than any other approach that could have been taken. The graph showed the difference in mortality between the treated and control groups in the different trials expressed as the number of babies saved by the surfactant treatment per 100 babies treated. There were many different ways to express this data although none of them completely expressed the full effect. Britannia noted that the complainant offered no suggestion of a "less misleading" way of presenting the data. For example, if odds ratios had been used that would not have given the reader the simple and practical expression of how many babies were likely to be saved by the treatment. Britannia preferred to express the effect as the difference in mortality.

Case AUTH/642/11/97

COMPLAINT

Serono noted that the text above the table included the claim that Alec reduced neonatal mortality from 27% to 14%, but a reduction from 30% to 19% was shown in the table, from the same reference (the Ten Centre Trial). Serono considered this to be somewhat ambiguous and misleading. Further investigation of the reference revealed that one set of figures related to neonatal mortality at 28 days and the other to mortality in the neonatal unit (no time span given). This was not clear from the piece and therefore could be construed as misleading information. What was of greater concern was the implication that all figures quoted in the table were directly comparable and that the various categories contained a representative selection of surfactant preparations - this was clearly not the case.

Serono pointed out that the reduction in neonatal mortality from 30% to 19% related to death in the neonatal unit. However, the figures for other categories in the table were derived from this outcome at various time intervals (eg at 10 days, at 28 days, at hospital discharge). As was apparent from two sets of figures from the same reference these would vary according to when the outcome was measured. Serono considered that this made any comparison invalid and therefore the information presented in the table and bar chart represented misleading information in breach of Clause 7.2 of the Code.

RESPONSE

Britannia submitted that whilst it accepted that there might be some criticism relating to the lack of clarity in distinguishing between the figures relating to "neonatal mortality at 28 days" and "mortality in the neonatal unit", it did not regard this as being in any way misleading nor that there was a breach of the Code.

Britannia stated that although it accepted, for the reasons given by the complainant, that no perfect comparison between trials of different surfactants was possible, this was clearly a comparison that was of interest to clinicians. The data from available published trials had been presented in a manner which was no less satisfactory than any alternative means that could be envisaged. Britannia did not believe that there was any breach of Clause 7.2 of the Code.

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel noted that on page 2 of the mailer the effect of Alec on neonatal mortality was described as "... reduced neonatal mortality from 27% to 14%" which from the paper referenced related to mortality over 28 days (the Ten Centre Trial). The Panel assumed that the header "Alec reduced neonatal mortality by 48%" related to this finding, 14 being a 48% reduction from 27. The table of results presented figures of 30% and 19% for controls and Alec treated babies respectively and referenced the same paper as above (the Ten Centre Trial). These latter figures related to mortality in the neonatal unit. The bar chart depicted "Increased neonatal unit survival ..." and showed that for every 100 babies treated with Alec eleven more babies survived than might have been expected. The Panel assumed that this was the difference between 30 and 19.

The Panel noted that the table of results was introduced as comparing "... the effects of various surfactants on reported mortality". The figures for Alec related to mortality on the neonatal unit although this was not stated. Each of the figures for the other surfactant categories came from several references with no explanation in the mailer as to the time point for the stated mortality or how the results from the references had been combined to calculate the stated figures. The Panel was unable to tell how the figures had been calculated. The Panel noted that the mortality figures quoted for "All animal derived surfactants as rescue treatment" (30% in control group and 20% in the treated group) had come from an analysis of ten separate papers. The Panel noted that at least one of these papers (Horbar *et al* (1989)) referred to mortality at 7 and 28 days and did not quote a figure for mortality on the neonatal unit.

The Panel noted that the table was presented in such a way that readers would inevitably consider that the mortality figures were directly comparable although this was not the case.

The Panel noted that the bar chart below the table was derived from the figures in the table by a process of subtraction - mortality in controls minus mortality in treated - to give "increased neonatal unit survival". The Panel noted that the figures for Alec related to neonatal unit survival but that some of the other papers used in calculating figures given for the other surfactants had

used other time points.

The Panel considered that the layout of the data on page 2 would invite readers to make comparisons between the various surfactant groups and favourably compare Alec with the rest. Alec had not, however, been directly compared with any of the other surfactants. In the Panel's view there was no sound scientific basis for the figures given on page 2. Britannia had not offered an explanation as to how the figures had been calculated from the many references quoted and the Panel noted the company's submission that the data "had been presented in a manner no less satisfactory than any alternative means that could be envisaged". Overall the Panel considered the data presented was misleading and confusing and ruled a breach of Clause 7.2 of the Code.

b) Description "All animal derived surfactants as prophylactic treatment"

This description was used in both the table of results and the bar chart and results were given for this "category" of surfactant.

Case AUTH/629/10/97

COMPLAINT

The complainant used poractant alfa prophylactically in small babies and noted that this was excluded from the references given for "all animal derived surfactants".

RESPONSE

Britannia stated that the information in the table and bar chart was from published randomised controlled trials. There were no randomised controlled trials of poractant alfa used prophylactically. That was why there was no reference to poractant alfa in the references attached to "All animal derived surfactants as prophylactic treatment".

Case AUTH/642/11/97

COMPLAINT

Serono stated that the table and the bar chart referred to "All animal derived surfactants" which implied a representative sample of all natural surfactants. This was not so in the case of prophylactic treatment as Curosurf (poractant alfa) was not represented in this sample as borne out by the references.

RESPONSE

Britannia submitted that prophylactic use of Curosurf was not represented in the table and bar chart because there were no published randomised controlled trials of such use of that medicine. The company therefore did not accept Serono's implication that these data presentations could be misleading in breach of Clause 7.2 of the Code.

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel considered that use of the description "All animal derived surfactants as prophylactic treatment" would be taken by most readers to imply that all animal derived surfactants were included. This was not the case as poractant alfa (Curosurf) was not included due to a lack of data. The Panel considered that the description was misleading as alleged and ruled a breach of Clause 7.2 of the Code.

c) Claim "Alec reduces mortality at least as well as other surfactants when given at birth"

This claim appeared in the text above the table and bar chart.

Case AUTH/642/11/97

COMPLAINT

Serono alleged that the claim "Alec reduces mortality at least as well as other surfactants when given at birth", was not substantiated in the piece by any reference to a clinical paper in breach of Clause 7.3 of the Code. Furthermore, there were no trials to date that directly compared the mortality of Alec treated babies to Curosurf treated babies which would therefore make this a very difficult claim to substantiate. It was not appropriate to compare results from surfactant groups in individual trials (where they had been compared to placebo) as the indications for treatment might not have been the same and even where they were, these trials had differing inclusion criteria.

RESPONSE

Britannia submitted that Clause 7.3 of the Code required that claims and comparisons must be capable of substantiation, not that they must all actually be substantiated by references to clinical papers whenever they were made in promotional material. Britannia submitted that there was no breach of Clause 7.3 of the Code.

PANEL RULING

The Panel acknowledged that as far as the Code was concerned there was no need to reference the claim at issue as it did not refer to a published study. Information, claims and comparisons had to be capable of substantiation. The Panel noted the allegation that there was no data directly comparing Alec treated babies to Curosurf treated babies. Britannia had not responded on this point. The Panel noted that the claim in question appeared above the table on page 2 which compared the effects of various surfactants on reported mortality and assumed that the data therein supported the claim.

The Panel noted that the figures presented in the table had been calculated from many separate trials. There were no direct comparisons between the groups. In the Panel's view the claim implied that Alec had been directly compared with all other surfactants which was not so. The Panel considered that the claim had not been substantiated by the data presented and ruled a breach of Clause 7.3 of the Code.

d) Cochrane Collaboration

A table of results headed "The recently published Cochrane Collaboration meta-analysis comparing synthetic and animal derived surfactant showed no significant difference in mortality" appeared on page 3. The author of the report was Soll.

Case AUTH/629/10/97

COMPLAINT

The complainant noted that both poractant alfa and pumactant were missing from the analysis. As these were probably the two most widely used surfactants in the UK, the complainant did not see how Britannia could suggest that this supported its argument. The main conclusions of Soll were actually that "Both natural surfactant extracts and synthetic surfactant extracts are effective in the treatment of established respiratory distress syndrome. Comparative trials demonstrate greater early improvement in the requirement for ventilatory support and fewer pneumothoraces associated with natural surfactant extract treatment. On clinical grounds natural surfactant extracts would seem to be the more desirable choice". The complainant said that the mailer did not mention this, which was misleading.

RESPONSE

Britannia submitted that the table was taken from the Cochrane Database of Systematic Reviews for which the reference was given. It showed those trials that had specifically compared animal derived and synthetic surfactants. Poractant alfa and Alec were not included because there were no randomised trials comparing these with synthetic or animal derived surfactants respectively. Britannia was aware of the opinion of Soll but did not quote it because the mailer was only about mortality.

Britannia acknowledged that the complainant alleged that the table was somehow misleading because it did not quote Soll's comments even though they were related to matters other than mortality, but in Britannia's view this was going far beyond the requirements of the Code.

Britannia submitted that in relation to mortality, the published material had been presented accurately in the promotional item, and none of the information was misleading.

Case AUTH/642/11/97

COMPLAINT

Serono stated that the meta-analysis compared a range of animal derived surfactants to a single synthetic surfactant (colfosceril palmitate), not Alec, and indicated that there was a trend (although not statistically significant) towards reduced mortality with natural surfactant. This was not reflected in the mailer.

RESPONSE

Britannia submitted that the presentation of data was extracted from the Cochrane Database of Systematic Reviews (as referenced). It did not claim to be a full summary of the published data, but merely an abstract showing mortality data from those trials that had specifically compared animal derived and synthetic surfactants. Poractant alfa and Alec were not included because there were no randomised trials comparing these with synthetic or animal derived surfactants respectively - and there were no claims that any of the data related to Alec. In relation to mortality, the published material had been presented accurately in the promotional item, and none of the information was misleading. Serono's suggestion that a "trend" reported in the referenced article should be cited, even though it was not statistically significant, seemed inappropriate - and probably would have represented a breach of the Code. Britannia did not accept Serono's view that the presentation of this data was in any way misleading and submitted that there was no breach of Clause 7.2 of the Code.

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel noted that the Cochrane Collaboration report was a meta-analysis comparing synthetic and natural surfactants for a number of parameters including mortality in the treatment of established respiratory distress syndrome. It had not been made clear that the results presented were with respect to treatment with surfactants as opposed to prophylaxis. The Panel noted that Alec had not been included in the meta-analysis. The Panel considered, however, that inclusion of the results in a mailer for Alec would lead readers to assume that the results were applicable to Alec. The heading "... meta-analysis comparing synthetic and animal derived surfactant ..." implied that it was a comprehensive comparison of all synthetic surfactants vs all animal derived surfactants which was not so.

The Panel noted that the mailer had presented mortality data and with it the claim that "synthetic and animal derived surfactant showed no significant difference in mortality". The report from which the data had been taken, however, stated that "A trend towards reduced mortality is noted in association with natural surfactant extract treatment". The original report also stated in its conclusion that "On clinical grounds, natural surfactant extract would seem to be the more desirable choice when compared to currently available synthetic surfactants". The Panel considered that the author of the Cochrane report favoured natural surfactants over synthetic agents although the data had been presented in the mailer in support of a claim of equivalence between the two types of surfactant. The Panel considered that the mailer had not accurately reflected the conclusions of the Cochrane report and ruled a breach of Clause 7.2 of the Code.

3 Claim referring to Alec as "... being the most frequently used surfactant in the UK"

This claim appeared at the bottom of page 3 beneath the data from the Cochrane Collaboration.

Case AUTH/642/11/97

COMPLAINT

Serono alleged that the claim was unsubstantiated by the reference quoted as closer examination of the IMS British Hospital Index (which was a quarterly publication) revealed that in the fourth quarter 1996 Alec and Curosurf sold 1,900 and 2,400 units respectively. In the whole year 1996 Alec and Curosurf both sold 6,100 units. These sets of figures were published in February 1997.

Serono stated that it was possible that the reference given by Britannia might relate to the Monthly Maxims data that IMS produced; however, this was wholly unsuitable for substantiating a major claim as it was a snapshot view of one month, produced two months in arrears. Additionally, figures for December 1996 and before related to sales of product into hospitals and not usage. IMS data published in February 1997 could only relate to this period.

RESPONSE

Britannia submitted data from the IMS Hospital Pharmacy Audit Index which tracked the usage of products from pharmacy to the wards. Figures were given for the fourth quarter 1996 which showed that 1,669 units of Alec had been used compared to 1,571 units of poractant alpha, for the whole of 1996 the figures were 5,802 and 5,587 respectively. Britannia contended that Alec was the most frequently used surfactant and therefore the claim could be substantiated.

PANEL RULING

The Panel considered that this allegation was more appropriately dealt with under Clause 7.8 of the Code which stated that superlatives could be used only in those limited circumstances where they related to a clear fact about a medicine. The supplementary information gave further guidance that the use of a superlative that could be substantiated was a simple statement of fact which could be very clearly demonstrated.

The Panel noted that Serono had provided sales data showing that in 1996 the same number of units of Alec and poractant alfa were sold. Britannia had provided data relating to the movement of medicines from the pharmacy to the ward. In this case the data showed that in 1996 more units of Alec were moved than poractant alpha. The Panel considered that while the data provided by Britannia was more relevant to the actual use of a product than the sales data provided by Serono, the situation seemed to be fairly dynamic. From the data supplied by Britannia the Panel noted that in 1996 there were four months when more units of Curosurf than Alec had been used and one month where the number of units used was within 2 of each other. Figures for January and February 1997 showed more units of Curosurf than Alec being used in February. The Panel decided that the claim that Alec was the most frequently used surfactant in the UK was not a simple statement of fact that could be very clearly demonstrated. The Panel ruled a breach of Clause 7.8 of the Code.

4 Claim "reduced parenchymal brain haemorrhages by 33%"

Page 4 of the mailer summarised the advantages of Alec in a number of bullet points and included this claim.

Case AUTH/629/10/97

COMPLAINT

The complainant stated that on examining the published results of the multicentre trial from which the claim was derived it was apparent that the reduction of brain haemorrhages was not statistically significant ($p<0.07$) [the published paper stated $p=0.06$]. Furthermore the reduction was only achieved in Cambridge and there was an identical rate of haemorrhage (18%) in treated infants and controls in the other centres. Also, in the sub-group of 25-26 week gestation there was a very similar rate (32% in controls vs 33% in treated infants).

RESPONSE

Britannia submitted that the claim was referenced to a publication in the British Medical Journal and stated that this was the factual finding of that trial and it had been reported accurately. Britannia had not made a general statement that "Alec reduces ..", since this was the finding of a subgroup analysis in a single trial. The nature of this subgroup analysis was such that a significance level of $p=0.07$ would be considered as "worthy of note". Britannia contended that this statement was not misleading, but was fair and balanced, and hence not in breach of the Code.

Case AUTH/642/11/97

COMPLAINT

Serono stated that the mailer quoted a reduction of 33% in parenchymal brain haemorrhage referenced to the Ten Centre Study. On close examination of the figures it was apparent that the differences reported in the overall rates were only at the Cambridge centre and that overall there was no difference at "non-Cambridge" centres. In other words, the claimed reduction in brain haemorrhage appeared to be based on the results of a cohort of babies treated at a single centre in the study; this result had not been reproduced elsewhere. Serono alleged that this constituted misrepresentation of the literature in breach of Clause 7.2 of the Code.

RESPONSE

Britannia contended that there appeared to be no case to answer. The promotional material reported correctly the overall finding of the published trial; the fact that an identifiable subgroup of the patients was predominantly responsible for this finding did not alter the fact that the overall finding was correctly represented. Britannia denied a breach of Clause 7.2 of the Code.

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel noted that the paper supporting this claim stated that Alec reduced the incidence of parenchymal haemorrhages from 24% to 16% ie, a reduction of 33%, but that this reduction was not statistically significant (p=0.06). The Panel also noted that the paper included a further analysis of the data which showed that babies treated in centres other than Cambridge had no reduction in the incidence of parenchymal haemorrhages (18% in controls and 18% in treated). The reported overall reduction of 33% therefore appeared to be due to the sub-set of babies treated in Cambridge (30% in controls and 14% in treated).

The Panel considered that although the claim accurately reflected the findings of the Ten Centre Study, the clinical importance of those findings would not be apparent to the reader in the broad claim that Alec "reduced parenchymal brain haemorrhages by 33%". The finding had not been set in its clinical context. The Panel considered that the claim was therefore misleading and ruled a breach of Clause 7.2 of the Code.

5 Claim "improved compliance by 50% within 6 hours"

This claim for Alec was included as a bullet point on page 4 of the mailer.

Case AUTH/642/11/97

COMPLAINT

Serono stated that in the article from which the claim of "improved compliance by 50% within 6 hours" was taken, the Alec receiving group was compared to a group receiving saline placebo, rather than pre- and post-treatment values being compared. Therefore although the results might represent a difference between the two groups, the claim of "improvement" was unsubstantiated as there were no pre-treatment baseline measurements for comparison. This was not stated in the piece and therefore represented misrepresentation of the data in breach of Clause 7.2 of the Code. Serono added that the claim constituted promotion outside of the licence in breach of Clause 3.2 of the Code as the prescribing information on the back of this piece clearly stated "... gestational age 25 to 29 weeks ..." and not 23-29 weeks as was the subgroup used to substantiate the claim.

RESPONSE

Britannia stated that in the study in question it was not possible to compare pre- and post-treatment compliance figures within individual patients, since Alec was administered at the time of the first breath. For this reason, a parallel-group comparison was undertaken, comparing the subsequent lung compliance of babies who had been treated with Alec and placebo (at birth). This was standard methodology in such situations. The comparison between two groups was generally accepted as the nearest possible surrogate measure of (unmeasurable) within-patient changes. Accordingly, the statements with the phrases "improvement" and "deterioration" had accepted meaning in this situation.

By way of illustration Britannia put forward the hypothetical promotional claim "operation A resulted in an improvement in survival as compared with operation B" stating that this was perfectly acceptable and unambiguous, even though no single patient could have two operations, or die twice.

Britannia therefore contended that there was no misrepresentation of the data, and thus no breach of Clause 7.2 of the Code.

Britannia acknowledged that the trial included babies under 25 weeks' gestation but submitted that there was no attempt to promote the use of Alec in this age group. The prescribing information clearly stated the patient population for which Alec could be used. Britannia denied a breach of Clause 3.2 of the Code.

PANEL RULING

The Panel considered it was reasonable to use a comparison with a control group to compare compliance rather than a pre- and post-treatment group. The Panel did not consider that the claim was misleading because of the trial design and no breach of the Code was ruled in that regard. The Panel noted, however, that no comparator was given in the claim. The main thrust of the mailer had been to compare Alec with other surfactants. There was no statement, however, that the respiratory compliance results were achieved versus placebo. The Panel considered that this was misleading in breach of Clause 7.2 of the Code.

The Panel noted that claim was supported by data in babies of a gestational age of 23-29 weeks. Alec was for use in babies of 25-29 weeks. The Panel noted that the mailer did not refer to babies of less than 25 weeks and considered, therefore, that the claim did not constitute promotion outside the licence. No breach of Clause 3.2 was ruled.

6 Use of hanging comparisons

Page 4 of the mailer carried a number of claims for Alec such as "reduced neonatal mortality...", "reduced incidence and severity of RDS" etc.

Case AUTH/629/10/97

COMPLAINT

The complainant noted that the mailer seemed to be comparing Alec with other surfactants. Conversely the claims about Alec on page 4 were in comparison to control, although the cited references had to be read to establish this.

RESPONSE

Britannia did not respond to this point.

Case AUTH/642/11/97

COMPLAINT

Serono stated that the use of hanging comparisons "reduced neonatal mortality", "reduced incidence and severity of RDS" etc and the claim "Improved compliance by 50%" breached Clause 7.2 of the Code as the comparator was not stated.

RESPONSE

Britannia submitted that Serono was mistaken in its assertions that the words "reduced" and "improved" were being used as comparative adjectives, whereas they were, in fact, being used as verbs (past tense). The intended meanings, which appeared to be understood by the majority of readers were "(Alec) reduced incidence and severity of RDS", "(Alec) improved compliance by 50%" etc. In fact, these past tense verbs were substituted for present tense ones ("reduces" and "improves") at the request of one of the signatories who approved these items of promotional material, in order to clarify that the statements related to the results of specific clinical trials (all referenced), rather than being general statements about the product.

Britannia submitted that since no comparisons were being made, "hanging" or otherwise, there was no breach of Clause 7.2 of the Code as alleged.

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel noted that pages 2 and 3 of the mailer compared Alec with other surfactants. Page 4 contained a series of claims, such as "reduced neonatal mortality by 48%", "reduced ventilation time", "improved compliance by 50% within 6 hours", "reduced time in supplemental oxygen" etc. There was no statement that these results were achieved versus placebo. The Panel considered that it was arguable as to whether the claims were strictly "hanging comparisons" but given that the main thrust of the mailer was to compare Alec with other surfactants it was misleading not to state that the comparator for the claims made on page 4 was placebo. A breach of Clause 7.2 of the Code was ruled.

7 No reference as to where prescribing information could be found

Case AUTH/642/11/97

COMPLAINT

Serono stated that in this multi-page piece there was no indication as to where the prescribing information might be found in breach of Clause 4.6 of the Code.

RESPONSE

Britannia submitted that the mailer was a single piece of card, folded so as to divide it into six sections (not pages), with an obvious "front" and "back", with the required prescribing information on the "back".

Britannia did not consider that this constituted an "item of four or more pages", in the sense intended by the Code (eg for multi-page journal advertisements) and that the "obvious positioning" of prescribing information on the back of the item was in keeping with the spirit of the Code. Britannia contended that such an "indication" was not required by the Code for the item in question, and that there was no breach of Clause 4.6 of the Code.

PANEL RULING

The Panel noted that Clause 4.6 of the Code required that in the case of printed promotional material consisting of more than four pages, a clear reference must be given to where the prescribing information could be found. The mailer in question consisted of four pages, a half page flap and a detachable reply paid card. The mailer thus consisted of more than four pages but there was no reference as to where prescribing information could be found. The Panel therefore ruled a breach of Clause 4.6 of the Code.

The Panel noted that there appeared to be a misunderstanding on the part of Britannia as it was not possible under the Code to have a journal advertisement consisting of four or more pages. The maximum length of a journal advertisement was two consecutive pages (Clause 6.1).

B Mailer entitled "The Advantages of Alec" (AL.ML-ADV.VI)

This was a four page mailer which had two flaps, one of which was a detachable reply paid card whilst the other was essentially an extension of pages 3 and 4 and had been used to list the 25 references cited in the piece. Britannia did not state to whom the mailer had been sent but Serono stated that it had been available on an exhibition stand.

1 Claim "The two phospholipids in Alec, dipalmitoylphosphatidylcholine (DPPC) and unsaturated phosphatidylglycerol (PG), are a simple replacement for the two phospholipids which are deficient in the lungs of premature babies"

Case AUTH/629/10/97

COMPLAINT

The complainant stated that the mailer implied that Alec simply replaced the two phospholipids that were absent in premature babies. This was quite misleading as it implied that these were the only components that were missing. Surfactant could be isolated in babies from about week 23 onwards, however many components were either absent or in the incorrect proportion compared with adult 'mature' surfactant. The mailer failed to explain that the surfactant specific proteins were also important in the functional nature of this immature surfactant and that, if they were missing, it was unlikely that a surfactant that

did not contain them would actually adequately lower surface tension. Phosphatidylglycerol was produced quite late in gestation, as phosphatidylinositol seemed to be produced preferentially earlier on. Phosphatidylinositol had been shown to substitute for phosphatidylglycerol in its functional role.

RESPONSE

Britannia submitted that the mailer did not imply that Alec replaced the two phospholipids that were absent in premature babies as claimed by the complainant. It stated "... the two phospholipids in Alec are a simple replacement for the two phospholipids which are deficient in the lungs of premature babies". It was wrong to say that this implied that these were the only two components that were missing.

Britannia contended that the role of surfactant specific proteins was not part of this section which dealt solely with lipids. The claim was not misleading and there was no breach of the Code.

PANEL RULING

The Panel noted that the claim appeared in a section of text headed "A Pure and Simple Surfactant". The Panel considered that some readers might assume from the claim "The two phospholipids in Alec ... are a simple replacement for the two phospholipids which are deficient in the lungs of premature babies" that Alec simply restored the babies' lungs to 'normal' by replacing what was missing. This was not so, the situation was much more complex. The Panel considered that because the claim was an over simplification of what was a complicated area of medicine it was misleading. The Panel ruled a breach of Clause 7.2 of the Code.

2 Claim "The clinical trials undertaken with Alec reflect clinical practice. The only exclusion was lethal congenital malformations [referenced to the Cambridge-Nottingham trial and the Ten Centre Trial]. This means that the results can be applied directly to the effect of Alec when used in clinical practice"

Case AUTH/629/10/97

COMPLAINT

The complainant stated that to suggest that the results of the Alec trials could be applied directly to clinical practice was total rubbish. All randomised trials, by definition, were only a representation. In normal clinical practice babies would not be randomised and care tended to be very much tailored to individual babies, according to their unique situation. In trials, protocols were adopted which allowed the results of two or more matched groups to be compared. This removed much of the individual attention to care. Additionally, as the Ten Centre Trial was passed by an ethics committee, the complainant could only assume that full written parental consent must have been obtained. If this was the case there would be a proportion of babies that were not consented and these would need to be accounted for to ensure that they did not represent a homogeneous group that was being overlooked in the final analysis. The trial made no reference to this and so it would be impossible to establish whether the study group represented a 'normal' clinical workload.

RESPONSE

Britannia stated that the Ten Centre Trial was specifically designed to enrol all babies whatever their problems, apart from lethal congenital abnormalities. The purpose was to include the sickest babies that neonatal paediatricians might want to treat with surfactant whatever their problems. It was therefore correct to say that this closely reflected clinical practice which was in contrast to most of the trials of surfactant that had enrolled from highly selective groups of babies. As this was a large trial the groups were, therefore, appropriately matched. The trial did not keep a record of those babies cared for in the ten units who were not enrolled in the trial.

Britannia submitted that the point being made in the mailer was that the trials of Alec were far less restrictive in their entry criterion than most other surfactant trials. As such the results could more readily be extrapolated to clinical practice than would be the case with many of the other surfactant trials. It was not claimed that the study group represented a "normal clinical work load". Britannia did not agree with the complainant who was suggesting that doctors would be 'misled' into believing that any clinical trial was a perfect representation of clinical practice. The claims were not misleading, and therefore, not in breach of the Code.

PANEL RULING

The Panel accepted that the clinical trials with Alec had less restrictive entry criteria than studies with other surfactants. The Panel noted that two clinical papers were referenced in the mailer. Describing the Cambridge-Nottingham trial, Morley *et al* stated that "Randomized inclusion of all babies ... means that the results reflect the effect this surfactant would produce in routine clinical practice". In a discussion of the statistical analysis, however, it was stated that "... the outcome data are skewed because half the babies had no respiratory problems". The Ten Centre Trial was described by its authors as giving "... a more realistic estimate of the clinical benefits of surfactant". In the discussion of the Ten Centre Trial design the authors stated that "... the results of a trial are only estimates of the real effect". The Panel considered that given the comments in the clinical papers, the claim that the clinical trials results could be "applied directly to the effect of Alec when used in clinical practice" overstated the position and was misleading. The Panel ruled a breach of Clause 7.2 of the Code.

3 Separation of study results and promotion outside the licence

In a section headed "Improved survival by 48%", results from the Ten Centre Trial were given and referenced to one paper. This was followed by a paragraph giving the results from the Cambridge-Nottingham trial. It was stated that the Cambridge-Nottingham trial was in babies of 23 to 30 weeks' gestation.

Case AUTH/629/10/97

COMPLAINT

The complainant noted that Britannia had separated the results of the Ten Centre Trial and the Cambridge-Nottingham Trial so suggesting that the results confirmed each other when in fact the babies from the latter trial subsequently formed part of the former trial. In neonatology it was not uncommon to use drugs that were unlicensed, really just reflecting that it was very difficult to get ethical approval for trials involving premature babies. The complainant considered, however, that it was slightly unethical for companies to promote their medicines for indications that they were not licensed for. Alec was licensed for babies of 25 to 29 weeks' gestation only and yet Britannia appeared to be encouraging its use from 23 weeks, at which there was little evidence that surfactant therapy of any form was effective. The complainant noted that the non-Cambridge data on survival in the Ten Centre Trial showed that mortality on the unit in the treatment and control groups in the 25-26 week range were very similar at 44% and 50% respectively (table II in the paper suggested that mortality was higher in the Alec treated group than in controls, 44% and 41% respectively) and this was certainly very different from the large reduction suggested by the trial overall. This made the statement about reduction in neonatal mortality difficult to confirm and at the very least made this a very unsuitable and unreliable paper to make claims from.

RESPONSE

Britannia confirmed that the mailer stated that the enrolment of babies in the Cambridge-Nottingham Trial was from 23 weeks' gestation. That was a fact and there was no promotion of Alec in babies less than 25 weeks' gestation. The data sheet was specific about the use in 25 to 29 week gestation babies.

Britannia stated that the Ten Centre Trial presented data in different stratified groups for the readers. It was not designed specifically to analyse these subgroups and did not have sufficient power to do so. The trial reported its primary aim: the overall effect on mortality. There was nothing misleading in the statements and there was no breach of the Code.

Case AUTH/642/11/97

COMPLAINT

Serono alleged that the claim "... in babies of 23 to 30 weeks' gestation the overall mortality was reduced from 36% to 17% by using Alec" constituted promotion outside of the licence in breach of Clause 3.2 of the Code. Prescribing information on the back of the piece clearly stated "... gestational age 25 to 29 weeks ...".

RESPONSE

Britannia stated that there was no attempt to promote the use in babies under 25 weeks' gestation. A statement of fact was made regarding the gestational age of babies in the referenced clinical trial. Indeed, to present the results of that trial without mention of the nature of the patient population would possibly have represented a violation of Clause 7 of the Code. The mailer contained prescribing information that clearly indicated the patient group for which Alec was licensed and for which its use was being promoted.

Britannia stated that while one of the referenced trials related to babies with gestational ages of 23-29 weeks the prescribing information included in the mailer correctly specified the range of gestational ages for which Alec might be used. In none of the items was there any attempt to promote the use of Alec in any other patient group. Accordingly there was no breach of Clause 3.2 of the Code.

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel noted that the mailing gave mortality results from the Ten Centre Trial and in a separate paragraph mortality results from the Cambridge-Nottingham trial. Each paragraph was referenced to a separate trial. The Panel considered that many readers would be misled into assuming that these were two separate trials, the results of one confirming the results of the other. This was not so. The Panel considered that the presentation of the data was misleading and ruled a breach of Clause 7.2 of the Code.

The Panel noted that Alec was indicated for use in babies of an estimated gestational age of 25-29 weeks. The Panel considered that the inclusion of the statement "In the Cambridge-Nottingham trial in babies of 23 to 30 weeks' gestation the overall mortality was reduced from 36% to 17% by using Alec" was misleading. The Panel ruled a breach of Clause 7.2 of the Code. The Panel did not consider that the statement constituted promotion outside the licence. No breach of Clause 3.2 was ruled.

4 Claim "Alec reduces mortality at least as well as other surfactants given at birth"

This was the final claim under the heading of "Improved survival by 48%".

Case AUTH/642/11/97

COMPLAINT

Serono stated that the claim was not substantiated in the piece by any reference to a clinical paper in breach of Clause 7.3 of the Code.

Serono stated that there were no trials to date that directly compared the mortality of Alec treated babies to Curosurf treated babies which would therefore make this a very difficult statement to substantiate. It was not appropriate to compare results from surfactants groups in individual trials (where they had been compared to placebo) as the indications for treatment might not be the same and even where they were, these trials had differing inclusion criteria. This very point was actually raised earlier in the mailer when it was stated that "Most trials with other

surfactants have studied highly selected groups of babies".

RESPONSE

Britannia submitted that Clause 7.3 of the Code required that claims and comparisons must be capable of substantiation, not that they must all actually be substantiated by references to clinical papers whenever they are made in promotional material. Britannia contended that there was no breach of Clause 7.3 of the Code.

PANEL RULING

The Panel noted that this allegation was similar to one made about mailer A (point A2(c)) although the context of the claim was different.

The Panel noted its views in allegation A2(c) that: "The Panel acknowledged that as far as the Code was concerned there was no need to reference the claim at issue as it did not refer to a published study. Information, claims and comparisons had to be capable of substantiation. The Panel noted the allegation that there was no data directly comparing Alec treated babies to Curosurf treated babies. Britannia had not responded on this point." also applied here.

In the Panel's view the claim now before it implied that Alec had been directly compared with all other surfactants which was not so. The Panel did not consider that indirect comparisons would provide substantiation as all studies varied particularly with regard to entry criteria. The Panel considered that the claim had not been substantiated and ruled a breach of Clause 7.3 of the Code.

5 Claim "Alec reduced brain haemorrhages"

Under the above claim it was stated that Alec reduced serious brain haemorrhages from 15% to 5% in the Cambridge - Nottingham trial and from 24% to 16% in the Ten Centre Trial. It was also stated that animal derived surfactants had not been shown to reduce the incidence of serious brain haemorrhage which was referenced to a Curosurf trial in babies with severe neonatal distress syndrome (Speer *et al* (1992)) and to a literature review (Gunkel & Banks (1993)).

Case AUTH/629/10/97

COMPLAINT

The complainant said that the section on brain haemorrhages was highly questionable. The use of two results was again misleading as the trials contained the same babies. The complainant was unable to find the figures of 15% and 5% in the reference quoted. The complainant used poractant alfa and noted the reference used to confirm the claims for Alec was in infants with established and severe respiratory distress syndrome. The complainant submitted that to see huge reductions in complications in this type of group was unlikely. Alec was recommended for prophylaxis and yet Britannia was using a "rescue" paper for comparison. Recent prophylaxis papers had shown beneficial effects of natural surfactants used prophylactically (for example Walti H *et al* (1995)).

RESPONSE

Britannia submitted that the claim, "Alec reduced serious brain haemorrhages from 15% to 5%, in the Cambridge-Nottingham trial" was correct and referred to the reduction in haemorrhages shown in Table V of the paper. The control group had 21 serious haemorrhages (7 grade 2 and 3, 13 grade 4 and 1 at postmortem) compared with 7 in the surfactant treated group (4 grade 2 and 3, 2 grade 4 and 1 at postmortem). This was 21/139 (15%) and 7/137 (5%).

Britannia stated that the statement concerning the findings of animal derived surfactants was supported by a published paper which set out all the information from different randomised trials about the effect of surfactant on intracranial haemorrhage. The randomised, controlled trials of animal derived surfactant had not been shown to reduce the incidence of brain haemorrhages.

Britannia stated that the trial quoted by the complainant (Walti H *et al* (1995)) was not a relevant trial in this context because it was a trial where all the babies were treated with poractant alfa. It simply compared prophylaxis versus rescue treatment.

Case AUTH/642/11/97

COMPLAINT

Serono noted that the mailer quoted a reduction of intraventricular haemorrhage from 24% in the saline placebo group to 16% in the Alec treated group in the Ten Centre Trial. On close examination of the figures, however, it was apparent that the differences reported in the overall rates were due to the rates reported at the Cambridge centre. At non-Cambridge centres there was no difference. This was not clear from the mailer. The figures were given for the groups as follows: Cambridge: control 30%; Alec 14%; non-Cambridge: control 18%, Alec 18%; overall: control 24%, Alec 16%.

Serono stated that it was not clear from the mailer that one third of the babies were treated at the Cambridge Centre and furthermore these same babies were represented in both the two and ten centre studies referenced in the mailer. In other words, the claimed reduction in brain haemorrhage appeared to be based on the results of a cohort of babies treated at a single centre; this result had not been reproduced elsewhere. Serono alleged that this constituted misrepresentation of the literature in breach of Clause 7.2 of the Code.

Serono also stated that the figures for reduction of serious brain haemorrhage from 15% to 5% were not clear from the reference given and so the claim was unsubstantiated in breach of Clause 7.3 of the Code. In the quoted two-centre study in Cambridge and Nottingham, 18% and 8% were mentioned (in table II of this article).

In addition, Serono noted that the mailer claimed that the reduction in serious brain haemorrhage had not been demonstrated with animal-derived surfactants and gave two references (Speer *et al* (1992) and Gunkel and Banks

(1993)). Serono alleged that this was a misrepresentation of the current literature.

Serono noted that the Curosurf paper cited (Speer *et al* (1992)) was a comparison between single and multiple doses in rescue treatment (ie no control placebo group for comparison) and therefore a vast difference in the incidence of intraventricular haemorrhage in these two groups would not be anticipated, and it was not valid to compare the absolute values (%) obtained in this trial with those from the Alec trial, as the indications for treatment were not the same (Alec - prophylaxis vs Curosurf - rescue treatment, ie the Curosurf group represented a more sickly group of babies as they had actually developed respiratory distress syndrome).

Serono stated that in a recent multicentre trial comparing Curosurf prophylaxis with Curosurf rescue treatment (control) (Bevilacqua (1996)) there was a strong trend towards reduction of intraventricular haemorrhage in the prophylaxis group, but the p value just failed to show significance (p=0.52). In a similar study (Walti *et al* (1995)) the incidence of severe peri-intraventricular haemorrhage was significantly decreased in the Curosurf prophylaxis group compared to Curosurf rescue treatment; this was due to a significant difference in the incidence of severe intraventricular haemorrhage in the subset of babies (approx 2/3 of total) who were born at units not participating in the study, and then transferred to one of the study centres.

Serono stated that the important messages from the second article cited by Britannia (Gunkel and Banks (1993)) were that the majority of studies comparing surfactant with control had shown no difference in rates of intracranial haemorrhage; and that careful management of ventilation and oxygenation might be important in the prevention of intraventricular haemorrhage. The importance of this was apparent if one considered the subgroup analysis in the Ten Centre Trial as set out above.

RESPONSE

With regard to the figures for reduction in serious brain haemorrhage, Britannia pointed out that table II (Cambridge-Nottingham trial) as referred to by Serono reported all brain haemorrhages, not just serious brain haemorrhages. The data for severe brain haemorrhages was in table V. Severe brain haemorrhages were grades 2, 3, 4 and found at post-mortem. In the control group this was 21/139 (15.1%) and for the surfactant treated group 7/137 (5.1%). Therefore this was not an unsubstantiated claim.

Britannia submitted that the claim in the mailer, "Animal derived surfactants have not been shown to reduce serious brain haemorrhage", was correct and well borne out by the published literature and the results for the randomised controlled clinical trials. There were no papers or claims from Curosurf or Survanta that the treatment significantly reduced serious brain haemorrhages. Britannia pointed out that Serono confirmed this in its statement, "... the majority of studies comparing surfactant with control, have shown no difference in rates of intracranial haemorrhage".

Britannia submitted that Serono could not have it both ways in making its complaint, Serono was being selective about the use of data. Serono claimed that the Curosurf paper quoted was not appropriate because it was a trial of single versus multiple doses, rather than a placebo controlled trial. However, the company then went on to quote two Curosurf trials which were not placebo controlled and both compared prophylaxis versus rescue treatment. Serono reported that these showed that prophylactic Curosurf had a lower rate of severe intraventricular haemorrhage than rescue treatment. This was not evidence that Curosurf lowered the incidence of severe brain haemorrhages compared with controls.

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel noted that once again the results from the Cambridge-Nottingham trial and the Ten Centre Trial had been presented in a way which suggested that they were two separate studies, the results of one confirming the results of the other. This was not so (see point B3 above).

The Panel noted that the mailing stated that in the Cambridge-Nottingham trial Alec reduced serious brain haemorrhages from 15% to 5%. This result came from the Cambridge subgroup only, the technique to assess the grades of intraventricular haemorrhage was not available to the Nottingham centre.

The mailing also stated that Alec had reduced serious brain haemorrhages from 24% to 16% in the Ten Centre Trial. The Panel noted, however, that this reduction was not statistically significant (p=0.06) and appeared to be entirely due to the Cambridge sub-group. Non-Cambridge babies showed no decline in the incidence of brain haemorrhage (18% in treated and controls).

The Panel noted that the claim "Animal derived surfactants have not been shown to reduce the incidence of serious brain damage" was referenced to two papers. The first compared the effects of single or multiple doses of Curosurf in babies with severe respiratory distress syndrome. The Panel noted that this was a different patient population to those in the Ten Centre Trial. Babies in the Ten Centre Trial had received Alec as prophylaxis. The Panel also noted that the Ten Centre Trial compared a treatment group to a control group. The Curosurf trial had no control group. The Panel considered that the two trials were so different that their results with regard to brain haemorrhages could not be compared. The second paper was a review of surfactant studies with a particular emphasis on those involving beractant.

Overall the Panel considered that the way the data on brain haemorrhage was presented was misleading and gave undue weight to the limited positive data for Alec. The Panel therefore ruled a breach of Clause 7.2 of the Code.

6 Section headed "Alec improved lung function"

In a section headed "Alec improved lung function" the results of a trial (Morley & Greenhough (1991)) were given and it was claimed that in babies of less than 30 weeks' gestation Alec improved respiratory compliance by 50% within six hours. It was stated that animal derived

surfactants had not demonstrated such a large improvement in respiratory compliance.

Case AUTH/629/10/97

COMPLAINT

The complainant stated that the information in this section was very misleading. There was little question that it was animal derived surfactants that improved respiratory compliance very shortly after administration and the changes in compliance with synthetic preparations were much slower. It was wrong to compare the results of the trials quoted as they were different in many ways. Uniquely, the Alec reference reported on the differences between two groups at certain time intervals. This was very unsatisfactory. It was far better to compare results before and after treatment, as in the other studies. Additionally, the Alec trial seemed to be a mixture of both static and dynamic compliance. It was difficult to see a scientific reason for combining the results of two wholly different measurements. This section was again about animal vs synthetic surfactants and it was again implied that the changes in incidence of babies with or without RDS were also comparing natural and synthetic surfactants when they were actually between Alec and control.

RESPONSE

Britannia stated that there was little evidence that animal derived surfactants improved compliance quickly in babies as stated by the complainant. In fact the clinical data which had been reported showed a slow change in compliance in contrast to the rapid changes in oxygenation. It was not possible to report change in compliance immediately the baby was born and incubated. The measurements of compliance were a mixture of static and dynamic compliance because some babies were spontaneously breathing and others were not. The strength of the study was that the measurements were made on both treated and control groups in the same way.

Britannia submitted that there were no comparative studies of animal derived surfactants and Alec on compliance and so it was not possible to compare them directly. The leaflet was correct in saying "Animal derived surfactants had not demonstrated such a large improvement in respiratory compliance" and was not misleading. There was no breach of the Code.

Case AUTH/642/11/97

COMPLAINT

Serono stated that in the paper from which the claim of "improved compliance by 50% within 6 hours" was taken, the Alec receiving group was compared to a group receiving saline placebo, rather than pre- and post-treatment values being compared. Therefore, although the results might represent a difference between the two groups, the claim of 'improvement' was unsubstantiated as there were no pre-treatment baseline measurements for comparison. This was not stated in the piece and therefore was a misrepresentation of the data in breach of Clause 7.2 of the Code. Furthermore, the claim constituted promotion outside of the licence, in breach of Clause 3.2, as the prescribing information on the back of the piece clearly stated "... gestational age 25 to 29 weeks ..." and not 23-29 weeks as was the subgroup used to substantiate the claim.

RESPONSE

Britannia stated that in the study in question it was not possible to compare pre-treatment and post-treatment compliance figures within individual patients, since Alec was administered at the time of the first breath. For this reason, a parallel-group comparison was undertaken, comparing the subsequent lung compliance of babies who had been treated with Alec and placebo (at birth). This was standard methodology in such situations. The comparison between two groups was generally accepted as the nearest possible surrogate measure of (unmeasurable) within-patient changes. Accordingly, the statements with the phrases 'improvement' and 'deterioration' had accepted meaning in this situation.

Britannia stated that by way of illustration one should imagine a hypothetical promotional claim in which a statement such as "operation A resulted in an improvement in survival as compared with operation B". This was perfectly acceptable and unambiguous, even though no single patient could have had two operations, or die twice.

Britannia contended that there was no misrepresentation of the data, and thus no breach of Clause 7.2 of the Code.

With regard to the alleged breach of Clause 3.2, Britannia stated that the complaint was on the fact that one of the referenced trials related to babies with gestational ages of 23-29 weeks. The included prescribing information correctly specified the range of gestational ages for which Alec might be used and there was no attempt to promote the use of Alec in any other patient group. Accordingly there was no breach of Clause 3.2 of the Code.

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel noted that this allegation was similar to one made about mailer A (point 5) although the context of the claims was different. The Panel noted that the paper from which the claim of improved compliance by 50% within 6 hours was taken reported a randomised trial in which babies of 23 to 29 weeks' gestation were given either Alec or saline control. Respiratory compliance was measured at 1, 6, 24, 48 and 168 hours after birth. The respiratory compliance of the controls increased gradually over seven days, whereas the compliance in the Alec treated group rose rapidly in the first six hours and then plateaued over the next seven days. Compared to the control group Alec-treated babies demonstrated significantly improved mean compliance at 6 and 24 hours. There was no difference between the groups at 1, 48 and 168 hours.

The Panel noted that at 6 hours compliance (ml/cm H_20/kg) was 0.91 in the Alec-treated group and 0.54 in the control group - a between group difference of 69%. At

168 hours compliance in the control group was 0.89 compared to 0.53 at one hour - a difference of 67%. Overall the Panel considered that the reference supported the claim being made and ruled no breach of Clause 7.2.

The Panel noted that the claim was supported by data in babies of a gestational age of 23-29 weeks. Alec was for use in babies of 25-29 weeks' gestation. The Panel noted that this section of the mailer only referred to babies of less than 30 weeks' gestation and considered, therefore, that the claim did not constitute promotion outside the licence. No breach of Clause 3.2 was ruled.

7 Claim "Alec has the smallest volume of any surfactant at 1.2ml per dose"

This claim appeared in a section headed "Ease of use".

Case AUTH/629/10/97

COMPLAINT

The complainant agreed that the volume of some surfactants did represent a challenge to the immature lung. The complainant noted that Alec was the only preparation that was not given on a per kilogram basis. The claim about being smallest seemed to be based on babies over a kilogram. At tertiary level centres staff cared for many very low birthweight babies and regularly saw babies of, say, 700g. The difference between a dose of poractant alfa and pumactant was not insignificant at this weight, 0.9ml and 1.2ml respectively.

RESPONSE

Britannia submitted that the claim that Alec had the smallest volume of any surfactant was a general reference to the average use of products. Alec was a single dose of 1.2ml. Other surfactants used 4ml/kg (beractant), 5ml/kg (colfosceril palmitate) and 1.25-2.5ml/kg (poractant alfa).

Britannia said that in referring to babies of 700g, the use might actually be in those babies less than 25 weeks' gestation for whom Alec was not licensed or promoted (so could not be compared). There was nothing misleading in this claim and there was no breach of the Code.

Case AUTH/642/11/97

COMPLAINT

Serono stated that the claim in question was inaccurate as the volume of a dose of Curosurf might be smaller; Curosurf was dosed on a per birthweight basis (from 1.25ml/kg) therefore for babies weighing less that 0.96kg, the volume of Curosurf would be less that 1.2ml. Serono provided a chart which showed that 50% of babies born at 26.5 weeks' and almost 97% of those born at 25 weeks' gestation were below 960g - this was not an insignificant proportion of babies eligible for treatment with Alec.

RESPONSE

Britannia submitted that the claim that Alec had the smallest volume of any surfactant was a general reference to the average use of products. Alec was a single dose of 1.2ml. Other surfactants used 4ml/kg (beractant), 5ml/kg (colfosceril palmitate) and 1.25-2.5ml/kg (poractant alfa).

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel noted that Alec was indicated for use in babies of an estimated gestational age of 25-29 weeks. The Panel noted that babies at the lower end of this age range were likely to weigh less than 1kg in which case the volume of Curosurf needed by these babies would be smaller than the volume of Alec. The Panel noted that in the Ten Centre Trial the mean birth weight for Alec treated babies of 25-26 weeks was 826g. These babies had been given 1.2ml of Alec. Such babies could have received Curosurf at a dose of 1.25ml/kg, ie 1ml. The Panel considered that for very small babies Alec did not have the smallest volume of any surfactant. The claim was therefore misleading and ruled in breach of Clause 7.2 of the Code.

8 Claim "Cardiorespiratory status maintained during administration"

Page 4 of the mailer summarised the advantages of Alec in a number of bullet points and included this claim. It was referenced to a paper by Ahluwalia and Morley (1995).

Case AUTH/629/10/97

COMPLAINT

The complainant noted that surfactant was given as a means of stabilising babies. When given as prophylaxis it was hoped that it would prevent the development of respiratory distress. The respiratory status of a baby was very rarely maintained during early administration as the act of instilling a liquid (a cold one, in the case of Alec), having first disconnected the baby from a ventilator, could be associated with immediate, if transient, hypoxia and bradycardia. The complainant's own studies had confirmed changes in blood pressure following disconnection for the administration of surfactant. The claim appeared to be based on administration at a median age of 26 hours in a very small, but diverse group of infants. It appeared that babies up to 37 weeks' gestation were included in this study and these were far less likely to exhibit changes in cardio-respiratory status.

RESPONSE

Britannia submitted that it was not possible to assess the immediate effect of surfactant treatment administered at birth. Despite the complainant's assertions based on his own studies (which might or might not be published), Alec had been shown not to destabilise the babies when given in the rescue mode. It would appear that whilst the complainant was challenging the study referenced (Ahluwalia and Morley (1995)), he did not actually suggest a breach of the Code.

PANEL RULING

The Panel considered that the cited reference supported the claim. The Panel noted, however, that although the mean age of the babies studied had been 28 weeks' gestation, babies of up to 37 weeks' gestation had been included in the trial. Alec was only for use in babies of 25-29 weeks' gestation. The Panel noted the complainant's submission that babies of up to 37 weeks' gestation were likely to be more stable than more premature babies. The Panel considered that the claim had been based on a patient population which included older, more stable, babies than those for which the product was indicated. The Panel considered that the claim was misleading and ruled a breach of Clause 7.2 of the Code.

9 Use of hanging comparisons

Page 4 of the mailer carried the same claims for Alec as page 4 of Mailer A.

Case AUTH/642/11/97

The Panel noted that Serono had repeated its allegations about hanging comparisons as set out in Mailer A point 6. The Panel considered that as the mailer in question also compared Alec with other surfactants its ruling of a breach of Clause 7.2 in point A6 also applied here.

10 No reference as to where prescribing information could be found

Case AUTH/642/11/97

The Panel noted that Serono had repeated its allegations about the lack of a reference to where the prescribing information could be found as set out in Mailer A point 7. The Panel considered that as the layout of Mailer B was similar to Mailer A, its ruling of a breach of Clause 4.6 of the Code in point A7 also applied here.

C Mailer entitled "Speed of Action" (AL.ML-SA.VI)

This was a four page mailer with a detachable reply paid card. Britannia did not state to whom the mailer had been sent but Serono stated that it had been available on an exhibition stand.

1 Claims "Alec treated babies had improved their respiratory compliance by 50% within 6 hours" and "... by 6 hours a baby treated at birth with Alec will have a 50% increase in tidal volume for the same ventilator pressure"

The first claim appeared at the top of page 2 above a graph depicting changes in respiratory compliance with time after Alec administration. The second claim was below the graph. Results with Alec were then compared with results from two other studies in which babies had been treated with animal derived surfactants.

Case AUTH/629/10/97

COMPLAINT

The complainant stated that this claim was a very misguided extrapolation of the changes in respiratory compliance. Tidal volume was the amount of air moved in and out of the lungs whereas respiratory compliance represented the change in lung volume for a given pressure. Following administration of surfactant, particularly natural surfactants, rapid improvements in compliance might be seen. These were certainly linked to changes in tidal volume but were by no means interchangeable. In addition to the tidal volume, an increase in functional residual capacity would also result in improved measurements of compliance.

The complainant stated again that the results of the Alec compliance study were incomparable with the other studies quoted.

RESPONSE

Britannia noted that the leaflet actually stated at the top of page two, "Alec treated babies had improved their respiratory compliance by 50% within 6 hours". The claim below the graph stated "This means that by 6 hours a baby treated at birth with Alec will have a 50% increase in tidal volume for the same ventilator pressure". Britannia said that this was used as an illustration to help the reader understand the change in compliance. It did not specifically claim "improvements in tidal volume of 50% with Alec". This was in no way misleading and there was no breach of the Code.

Case AUTH/642/11/97

COMPLAINT

Serono stated that the mailer claimed separately a 50% increase in respiratory compliance at 6 hours, and a 50% increase in tidal volume at 6 hours. For both of these claims it was not clear to what the comparisons were being made. A breach of Clause 7.2 of the Code was alleged.

Serono also stated that the 'tidal volume' statement constituted an unsubstantiated claim as no reference was given in breach of Clause 7.3 of the Code. It appeared to be related to the 'compliance graphic', however, the reference from which this data was taken reported only compliance and not tidal volume. As tidal volume was not equivalent to compliance it was not a valid extrapolation of the data. Compliance and tidal volume were different, although not entirely independent, entities.

Serono stated that the Alec and Curosurf compliance trials related to quite different patient populations - the indications for treatment were not the same (Alec - prophylaxis vs Curosurf - rescue treatment) and therefore the validity of any comparison was questionable, as rescue babies were, by definition, sicker as a group than the prophylaxis group.

Serono alleged that furthermore, the claim constituted promotion outside of the licence in breach of Clause 3.2 of

the Code as the prescribing information on the back of the piece clearly stated "... gestational age 25 to 29 weeks ..." and not 23-29 weeks as was the subgroup used to substantiate the claim.

Serono stated that the Alec study compared differences in compliance (actually a mixture of two differently measured forms of compliance) in Alec-treated babies to that measured in control (saline-treated) babies, whereas the Curosurf trial compared static compliance before treatment with static compliance after treatment, in the same babies. It was acknowledged in the Alec article that saline could damage the surfactant system and therefore the control group in this study was unlikely to show much improvement in compliance. Compliance was measured and expressed in a different way which further called into question the validity of any direct comparison between the two studies. In the Curosurf trial compliance was expressed in terms of length, but, in the Alec study, compliance was expressed in terms of weight. This could give different results and it was suggested that, in the case of compliance, expression in terms of length reflected a more informative measure than expression in terms of weight. Clearly this demonstrated that the two sets of measurements were not comparable. Comparability was implied in the piece and thus this constituted a misrepresentation of the literature in breach of Clause 7.2 of the Code.

RESPONSE

Britannia stated that in the study in question, it was not possible to compare pre- and post-treatment compliance figures within individual patients, since Alec was administered at the time of the first breath. For this reason, a parallel-group comparison was undertaken, comparing the subsequent lung compliance of babies who had been treated with Alec and placebo (at birth). This was standard methodology in such situations. The comparison between two groups was generally accepted as the nearest possible surrogate measure of (unmeasurable) within-patient changes. Accordingly, the statements with the phrases "improvement" and "deterioration" had accepted meaning in this situation.

By way of illustration Britannia put forward the hypothetical promotional claim "operation A resulted in an improvement in survival as compared with operation B" stating that this was perfectly acceptable and unambiguous, even though no single patient could have two operations, or die twice.

Britannia therefore contended that there was no misrepresentation of the data, and thus no breach of Clause 7.2 of the Code.

With regard to Serono's allegation of a breach of Clause 7.3 of the Code because the claim about tidal volume had not been substantiated, Britannia submitted that the Code did not require all statements to be referenced provided that they were capable of being substantiated. Britannia denied a breach of Clause 7.3 of the Code.

Britannia noted that the leaflet actually stated at the top of page two "Alec treated babies had improved their respiratory compliance by 50% within 6 hours". The claim below the graph stated "This means that by 6 hours a baby treated at birth with Alec will have a 50% increase in tidal volume for the same ventilator pressure". This was used as an illustration to help the reader understand the change in compliance. It did not specifically claim "improvements in tidal volume of 50% with Alec". This was in no way misleading and there was no breach of the Code.

Britannia noted that the mailer reported the effect of "natural" surfactants on compliance as published in three different papers. Britannia stated that Serono was correct in saying that the trials were on different patient populations. There were no trials directly comparing natural surfactants with Alec and so there was no other way of showing different effect of surfactant treatment on compliance. Different trials of surfactant therapy had used different entry criteria and therefore the severity of the illness of the patients in different trials was never exactly comparable. Britannia noted that Serono suggested, but did not produce any evidence, that the babies in the trials quoted were sicker than the babies in the Alec trial. The initial compliance measurements, an indicator of the severity of lung disease, were similar in the different trials and other parameters such as gestational age and oxygen requirements were also similar. Britannia had found no evidence that there was such a large difference between the babies in the trials that any comparison was invalid.

Britannia acknowledged that the trial included babies under 25 weeks' gestation but submitted that there was no attempt to promote the use of Alec in this age group. The prescribing information clearly stated the patient population for which Alec could be used. Britannia denied a breach of Clause 3.2 of the Code.

Britannia noted that Serono stated correctly that the Alec study compared the effect of Alec on compliance in treated babies and controls and the Curosurf study compared the effect before and after surfactant. The mailer showed changes in compliance with time, in the Alec study this was time after surfactant treatment at birth, in the Curosurf study this was time after surfactant administration. Britannia submitted that it was presenting the data as published and was not misleading.

Britannia noted Serono's comments about the Alec trial that "saline can damage the surfactant system and therefore the control group in this study were unlikely to show much improvement in compliance". That was controversial and unproven in this context. All ventilated babies had endotracheal toilet using instillation of a small amount of saline. No one had shown that it caused harm to the babies. Britannia stated that Serono missed the point; in these studies the controls received 1ml saline down the endotracheal tube but so did the Alec treated babies. So both groups had saline. All surfactants were mixed with saline and no one had shown that it was harmful.

Britannia stated that the trials used slightly different techniques and equipment for measuring compliance. However the results were similar. The technique used was not important in the context of this mailer because it was the change in the compliance which was being compared and different techniques would show changes if they were present.

Britannia stated that the mailer compared relative change in compliance measurements after surfactant treatment, not absolute values, and so whether the compliance was

expressed per kg body weight or length was not relevant. The relative change in compliance was reported in the Curosurf paper. This was not misleading, rather it made it easier for the reader.

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel considered that the layout of page 2 would lead most readers to assume that the statement regarding a 50% increase in tidal volume was a direct extrapolation of an improved respiratory compliance of 50%. The Panel noted that although respiratory compliance and tidal volume were connected they were not interchangeable. The Panel ruled that the statement regarding tidal volume was misleading in breach of Clause 7.2 of the Code.

The Panel noted that, in accordance with Clause 7.5 of the Code, references only need to be given when promotional material referred to published studies. The Panel noted that the claims regarding respiratory compliance did not refer to published studies and so no references were needed. With regard to the ability of the claims to be substantiated, the Panel considered that its ruling of a breach of Clause 7.2 covered the allegation of a breach of Clause 7.3 and made no ruling in this regard.

The Panel considered that the graph was clearly labelled such that it would be obvious that the claim regarding improved respiratory compliance was in comparison to control. The claim in that regard was not misleading and no breach of Clause 7.2 was ruled.

The Panel noted that below the two claims and the graph was a statement regarding changes in respiratory compliance observed with animal derived surfactants. The statement began "This effect on respiratory compliance compares with ..." thus inviting readers to directly compare the results observed with Alec and results observed with animal derived surfactants. The Panel noted that there had been no direct comparisons of Alec with animal derived surfactants. The implied comparison was thus misleading and a breach of Clause 7.2 was ruled.

The Panel noted that the babies in the Alec trial had an estimated gestational age of 23-29 weeks. Alec was for use in babies of 25-29 weeks. The Panel noted that the mailer did not refer to babies of less than 25 weeks and considered, therefore, that the claim did not constitute promotion outside the licence. No breach of Clause 3.2 was ruled.

2 Claim "Alec treatment has a gentle onset of action and does not destabilise the baby"

This was the last claim on page 2.

Case AUTH/642/11/97

COMPLAINT

Serono stated that the claim "Alec treatment has a gentle onset of action and ..." was not substantiated by the reference given, particularly as the study only took measurements until 15 minutes post treatment. Serono alleged a breach of Clause 7.3 of the Code.

RESPONSE

Britannia noted that the claim referred to by Serono continued "... does not destabilise the baby" and was referenced at that point. The reference therefore related to the second part of the claim (not quoted by Serono) and not the first - which was not referenced. Britannia contended that there was no requirement in the Code that every statement should be referenced, only that statements should be "capable of substantiation". Britannia stated that there was no breach of Clause 7.3 of the Code.

PANEL RULING

The Panel noted that the study cited in support of the claim had measured oxygenation and heart rate 15 minutes before, during and 15 minutes after the administration of a third dose of Alec. The median age of the babies had been 26 hours (range 21-43 hours). No clinically significant changes were seen in the mean values for oxygen saturation and heart rate either during or immediately after Alec administration. The Panel considered that the claim was thus substantiated by the reference given and no breach of Clause 7.3 was ruled.

3 Comparisons with animal derived surfactants

The text on page three consisted of a number of statements regarding animal derived surfactants which were referenced to eleven separate papers. The page ended with a general comparison of animal derived surfactants with Alec - "The rapid change in oxygenation seen in some babies after treatment with animal derived surfactants may cause problems and confer no extra benefits over the gentle onset of action of Alec".

Case AUTH/629/10/97

COMPLAINT

The complainant stated that page three of the mailer consisted of what could only be described as misleading scare-mongering about the use of natural surfactants. This was a good example of selectivity using aspects of individual papers, each with differing inclusion/exclusion criteria to justify claims that were not supported by other, and indeed more recent papers. The overall conclusion seemed to be that natural surfactants conferred no benefit in survival, although it was unclear whether Britannia was comparing this to Alec, no treatment, or synthetic surfactants in general. To the complainant's knowledge Alec had never been compared with any other surfactant and so any claim of improved or similar survival was totally unjustified.

Additionally, there was a suggestion that natural surfactants might cause problems that Alec did not. There was no reference to this claim and so it was difficult to know what 'problems' Britannia was referring to. The complainant had used natural surfactants for some four years and found their rapid onset of action a positive

advantage. It was certainly true that attention must be given to correct adjustment of oxygen and pressures following administration of surfactant; however, this was true of all surfactants and merely constituted proper attention to care. It was not the complainant's experience that natural surfactants caused any problems that were not encountered with synthetic preparations. The complainant had experience of using all four available preparations.

RESPONSE

Britannia stated that there could be no disparagement of other companies or their activities since neither were mentioned in any of the promotional items.

Britannia stated that the specific 'problems' referred to were all ones reported in the published material, which had been properly referenced. The reference to 'problems' in the second paragraph of the item was not, as suggested by the complainant, in any way vague - but in fact referred back to those specific (referenced) matters mentioned in the first paragraph.

Britannia noted that the complainant stated that "The overall conclusion seems to be that natural surfactants confer no benefit in survival ...". Unfortunately the complainant had omitted (or failed to notice) the word "added" before "benefit" and had presented anecdotal experiences to suggest that the (published and referenced) problems of natural surfactants were of no consequence. The comments in the promotional item merely reflected what had been published, and were in no way disparaging to competitive products.

Britannia stated that the information provided at the top of the third page of the leaflet was not controversial. It had all been reported in peer reviewed journals and was not (to the best of the company's knowledge) denied by the manufacturers of surfactant preparations. The reference in the leaflet to "Animal derived surfactants ... with no added benefit in survival" was made to two, large randomised, controlled trials of animal derived surfactant compared with the synthetic surfactant, colfosceril palmitate.

In the first trial by Horbar *et al* the deaths before discharge were 81/308 (26%) in babies treated with colfosceril palmitate and 70/306 (23%) with beractant (NS). In the second trial by the Vermont Oxford network the deaths before discharge were 121/644 (19%) for colfosceril palmitate and 108/652 (17%) for beractant (NS).

Alec had never been compared directly to any other surfactant. The leaflet did not claim or infer that it had.

The information relating to other surfactants had been reported accurately and fairly and there was no breach of the Code.

The "problems" of animal derived surfactants referred to in the second paragraph on the third page of the mailer were those "problems" which were set out in the previous paragraph. They were due to the rapid change in oxygenation seen in some babies after treatment with animal derived surfactants. There were no reports that Alec caused such problems despite the statement of the complainant.

PANEL RULING

The Panel noted that the paragraph detailing some of the problems associated with animal derived surfactants cited 11 clinical papers which reported results with Curosurf (porcine) or Survanta (bovine). Several statements were made about the various effects of these products, some of which were referenced only to Curosurf (flatten EEG, reduce blood pressure), and some only to Survanta, (destabilise cardio-respiratory function). All of the statements, however, appeared under the blanket term of animal derived surfactants. The last statement was that animal derived surfactants had "... no added benefit in survival" with no indication as to the comparator in this instance.

The Panel considered that the statement in the second paragraph "The rapid change in oxygenation seen in some babies after treatment with animal derived surfactants may cause problems and confer no extra benefits over the gentle onset of action of Alec" was vague. The Panel noted Britannia's submission that Alec had never been compared directly to any other surfactant and so considered that the comparison of animal derived surfactants with Alec was not supported by clinical data.

Overall the Panel considered this section of the leaflet to be unclear, inadequately supported by the data and therefore misleading. A breach of Clause 7.2 of the Code was ruled.

4 Hanging comparisons

Page 4 of the mailer carried the same claims for Alec as page 4 of Mailer A.

Case AUTH/642/11/97

The Panel noted that Serono repeated its allegations about hanging comparisons as set out in Mailer A point 6. The Panel considered that as the mailer in question also compared Alec with other surfactants, its ruling of a breach of Clause 7.2 in point A6 also applied here.

5 Claim "reduced parenchymal brain haemorrhages by 33%"

This claim was one of the bullet points included on page 4 of the mailer.

Case AUTH/642/11/97

The Panel noted that Serono repeated its allegation as set out in Mailer A point 4. The Panel considered that its ruling of a breach of Clause 7.2 in point A4 also applied here.

D Booklet entitled "Alec Administration Guide" (AL.AG.VI)

This twelve page booklet was a step-by-step guide to the preparation of reconstituted Alec and its subsequent administration. The back cover of the booklet carried a number of promotional claims for Alec which were identical to those on page 4 of Mailer A. Britannia did not state how the guide had been used.

1 Claim "reduced parenchymal brain haemorrhages by 33%"

Case AUTH/642/11/97

The Panel noted that Serono repeated its allegation as set out in Mailer A point 4. The Panel considered that its ruling of a breach of Clause 7.2 in point A4 also applied here.

2 Claim "Improved compliance by 50% within 6 hours"

Case AUTH/642/11/97

The Panel noted that Serono repeated its allegation as set out in Mailer A point 5. The Panel considered that its rulings of a breach of Clause 7.2 and no breach of Clause 3.2 in point A5 also applied here.

3 Hanging comparisons

Case AUTH/642/11/97

The Panel noted that Serono repeated its allegations about hanging comparisons as set out in Mailer A point 6. The Panel considered that as the Administration Guide made no mention of other surfactants the claims for Alec would be taken to be versus placebo, which was the case. No breach of Clause 7.2 was ruled.

The Panel noted that, notwithstanding the above ruling, the statement "reduced parenchymal brain haemorrhages by 33%" had been ruled to be in breach of Clause 7.2 of the Code for being misleading (see point A4).

E Folder entitled "A Pure & Simple Solution" (AL.FL.V1)

This A4 folder had a pocket on the inside page so that papers could be tucked inside. The back of the folder carried a number of promotional claims for Alec which were identical to those on page 4 of Mailer A. Britannia did not state how the folder had been used.

1 Claim "reduced parenchymal brain haemorrhages by 33%"

Case AUTH/642/11/97

The Panel noted that Serono repeated its allegation as set out in Mailer A point 4. The Panel considered that its ruling of a breach of Clause 7.2 in point A4 also applied here.

2 Claim "Improved compliance by 50% within 6 hours"

Case AUTH/642/11/97

The Panel noted that Serono repeated its allegation as set out in Mailer A point 5. The Panel considered that its rulings of a breach of Clause 7.2 and no breach of Clause 3.2 in point A5 also applied here.

3 Hanging comparisons

Case AUTH/642/11/97

The Panel noted that Serono repeated its allegations about hanging comparisons as set out in Mailer A point 6. The Panel considered that as the folder made no mention of other surfactants the claims for Alec would be taken to be versus placebo, which was the case. No breach of Clause 7.2 was ruled.

The Panel noted that, notwithstanding the above ruling, the statement "reduced parenchymal brain haemorrhages by 33%" had been ruled to be in breach of Clause 7.2 of the Code for being misleading (see point A4).

F Document entitled "Alec & Respiratory Distress Syndrome Summary of main clinical papers" (AL.CR.V1)

This was a four page A4 document which gave a brief description of Alec, a synopsis of two clinical trials with Alec and a review of the costs of surfactant treatment. The last page was headed "Alec - Main features" underneath which were eight stab points. Britannia did not state how the document had been used but Serono stated that it had been available on an exhibition stand.

1 Cost comparison

A cost comparison table compared the costs of colfosceril palmitate, poractant alfa, beractant and Alec. The cost of the single dose vials for each product were given in the first column of figures. Column two was headed "Recommended dose range" and the final column gave the "treatment cost range".

Case AUTH/629/10/97

COMPLAINT

The complainant stated that the table of cost of surfactant treatment was very misleading as the complainant did not believe that any of the surfactants were sold at the full price. The complainant had never been quoted the full price on any inquiries about cost. Further, the range of treatment costs seemed to suggest payment only for the amount of a vial of surfactant used; of course, the whole vial had to be paid for and anything left over from a part used vial had to be discarded.

It would be wrong to use the residual quantity as re-entry to the vial, or returning a warmed vial to the fridge, would not be consistent with the complainant's hospital's policy on reducing infections and the complainant considered that such action was not recommended by the individual companies.

RESPONSE

Britannia submitted that whilst it might be true that many surfactants were sold at contract prices, information on those prices did not exist in the public domain. However, users of products had an understandable interest in cost comparisons and the only basis on which an approximate idea of these could be presented was in terms of the

published prices. This was precisely what had been done in this mailer.

Britannia stated that the cost comparisons had been calculated on the basis of the appropriate and recommended administration instructions provided by the manufacturers. This was the least misleading way in which cost information could be presented, and was therefore, not in breach of the Code.

Case AUTH/642/11/97

COMPLAINT

Serono alleged that in the table of treatment cost ranges, the figures quoted for those products that were administered as a weight related dose were both inaccurate and misleading. It was not entirely clear how these costs had been calculated - Serono presumed on a neonate weighing one kilogram. However, the cost of treating such a child with Curosurf started at £400 (the cost of a 120mg vial), as it was a single-use vial of which the remainder must be discarded, and not the £333.33 stated, which implied that the remainder could be used subsequently. Serono considered this implication of multiple use of the vial to be misleading and alleged a breach of Clause 7.2 of the Code.

RESPONSE

Britannia stated that while the cost comparison chart did not take wastage from single use vials into account, clinicians were naturally interested in cost comparisons and the table in the promotional item had been presented in the fairest way possible, by quoting the pro-rata cost (at available published prices) of the dose range recommended by the respective manufacturers - which would, on average, fairly represent the cost of using the various drugs. Serono's specific objection to the fact that this approach had had the effect of reducing the bottom-of-range price of its product from £400 (the true price, when wastage was considered) to £333.33 seemed rather surprising. Britannia contended that it had presented the cost comparisons in the fairest way possible, which was not misleading and therefore not in breach of Clause 7.2 of the Code.

Cases AUTH/629/10/97 and AUTH/642/11/97

PANEL RULING

The Panel noted that the table compared the costs of four surfactants all of which were supplied in single use vials. The dose range for each was given which, for all but Alec, was expressed in terms of mg/kg. The dose of Alec was 100mg at a time irrespective of the baby's weight. The final treatment cost range was then stated. The Panel noted that the basis on which the final treatment costs had been calculated was not declared. The Panel assumed that it was based on treating a baby of 1kg.

The Panel noted that the final treatment costs included the cost of that part of a vial which would be used. Given that all of the surfactants were supplied in single use vials this was misleading as even if only half the vial was used the whole of it had to be paid for. The Panel noted that the result of this was that the lowest cost of three surfactants and the highest cost of two of them had been understated. The Panel noted that only the cost of Alec was correct for the dose range.

The Panel considered that the failure to state the basis on which the costs had been calculated and the inclusion of the costs of part used vials was misleading. A breach of Clause 7.2 was ruled.

The Panel considered that the cost comparison should be based, as it was, on the basic NHS costs. No breach of Clause 7.2 of the Code was ruled in that respect.

2 Claim "In a clinical trial Alec reduced the incidence of parenchymal brain haemorrhage from 24% to 16%"

Case AUTH/642/11/97

The Panel considered that this claim was equivalent to the claim that Alec "reduced parenchymal brain haemorrhages by 33%" as set out in Mailer A point 4. The Panel noted that Serono repeated its allegations as set out in Mailer A point 4. The Panel considered that its ruling of a breach of Clause 7.2 in point A4 also applied here.

3 Claim "This simple formulation avoids sensitisation of the lungs"

This claim was included as part of one of the eight "Main features" of Alec listed on the last page.

Case AUTH/629/10/97

COMPLAINT

The complainant knew of no published work looking at the immune response to Alec. There had been many studies looking at the likelihood of an immune response to the protein fractions of animal derived surfactants. The investigations had established that immune complexes to surfactant components could be identified in babies both receiving and not receiving surfactant replacements. Additionally, immune complexes could be formed to the lipid fraction of synthetic surfactants. This all seemed to be as a result of the lungs of preterm infants being rather 'leaky'. What any author or investigator (also borne out by clinical practice) had failed to show was any immune complex related damage. This was very much a question that was considered answered and was again an example of scaremongering aimed at those less familiar with surfactant as an academic topic. The complainant was uncertain how this formed part of a summary of main clinical papers when there was no paper on the subject in the summary.

RESPONSE

Britannia contended that the claim was demonstrably true - and did not necessarily imply that any other products necessarily sensitised the lungs. The point being made was that by choosing a protein-free surfactant one did not even have to consider the possibility of sensitisation.

There was nothing misleading or disparaging in this statement and hence there was no case to answer in terms of a claimed breach of the Code.

PANEL RULING

The Panel noted that in a description of Alec on page 2 of the document it was stated that the exclusion of animal derived proteins from the composition of Alec avoided the possibility of sensitisation of the lungs. The Panel noted that there appeared to be no data that sensitisation of the lungs with surfactants which contained animal derived proteins was a problem in practice. A paper supplied by Britannia which examined the use of Survanta stated that the evidence suggested that babies of less than 30 weeks' gestation did not produce antibodies to the animal proteins in the product.

The Panel noted that the claim in question "This simple formulation avoids sensitisation of the lungs" did not contain the word "possible". The Panel considered that if this was one of the main features of Alec then there was an implication that other surfactants definitely did cause sensitisation of the lungs which was not so. The Panel noted that one of the papers supplied by Britannia stated that Alec was unlikely to be harmful because of its lack of protein component. The Panel noted that Britannia did not submit any evidence that Alec definitely did not cause sensitisation of the lungs. The Panel considered that the statement that "This simple formulation avoids sensitisation of the lungs" was too strong given the evidence. In the Panel's view the difference was that with natural surfactants there was a possibility of sensitisation whereas with Alec this was unlikely. A breach of Clause 7.2 was ruled.

4 Claim "Administration of Alec is associated with minimal disturbance to the baby"

This claim was one of the eight given on the back page of the document. It was followed by the statement "a clinically important change in oxygenation or heart rate during or immediately after administration was not observed". The claim was referenced to Ahluwalia & Morley (1995).

Case AUTH/642/11/97

COMPLAINT

Serono stated that the claim and associated statement about heart rate and changes in oxygenation appeared to be based on a small population (21 babies) in somewhat unrepresentative circumstances. Further examination of the reference revealed that the results appeared to relate to subsequent (usually third) doses of Alec (ie, not the initial dose when the baby was most vulnerable) when the neonates were aged 21-43 hours (median 26 hours) and presumably stabilised to a certain degree; this was not clear from the claim. Serono considered that this was misrepresentation of the literature in breach of Clause 7.2.

Furthermore, Serono considered that the claim constituted promotion outside of the licence as the prescribing information on the back of this piece clearly stated "... gestational age 25 to 29 weeks ..." and not 25-37 weeks as is the population used to substantiate the claim.

RESPONSE

Britannia submitted that the referenced paper carefully examined the effect of a dose of Alec treatment on 21 babies ventilated for respiratory distress syndrome. Britannia noted that Serono suggested that this study was based on a small population in somewhat unrepresentative circumstances, but did not suggest how many patients should have been studied to produce a more satisfactory result or give reasons why this study was unsatisfactory. Britannia submitted that this was a very carefully organised study designed specifically to assess the effect of Alec administration and, as the results were similar in all the patients, 21 were enough to demonstrate the effect.

Britannia noted that Serono did not suggest why it considered the circumstances were unrepresentative. The paper stated the patients were "selected on the basis of clinically requiring surfactant therapy at the time that recording equipment was available". The babies were of varied gestational ages - 25 to 37 weeks, varied birth weights - 561 to 2680g and varied ventilator pressures - 16 to 40cm H_20 and inspired oxygen 0.30 to 0.98. Britannia considered that this showed they were very representative of the babies who were being treated with Alec.

Britannia stated that Serono was correct that the studies were mainly at the third dose of surfactant. This was for logistic reasons. It was impossible to study the before and after effects of the first dose of surfactant because it was given immediately at birth. The second dose was given at one hour when the child was still being stabilised and it was physically difficult to make the recordings. There was no evidence that the immediate effects of a third dose of surfactant were likely to be different from the second dose. This had not been reported for any surfactant. Britannia contended that the statement was true and did not misrepresent the literature.

Britannia noted that although the study included babies of gestational age up to 37 weeks, this was reported in the paper and not in the promotional literature. There was no breach of the Code.

Britannia noted that Serono had based its allegation of a breach of Clause 3.2 of the Code on the fact that one of the referenced trials related to babies with gestational ages of 23-29 weeks. The prescribing information included on the piece correctly specified the range of gestational ages for which Alec might be used and there was no attempt to promote the use of Alec in any other patient group. Accordingly there was no breach of Clause 3.2 of the Code.

PANEL RULING

The Panel noted that the cited paper had included babies of a gestational age of 25-37 weeks (median 28). Oxygenation and heart rate had usually been measured continually for 15 minutes before, during and 15 minutes after the administration of the third dose of Alec. The age of the babies at administration of Alec was 21-43 hours (median 26).

The Panel noted that the claim "Administration of Alec is associated with minimal disturbances to the baby" had not been put into context with respect to the gestational age of the babies or their age in hours. The Panel considered some readers would assume that the babies had been less than 30 weeks' gestation and that the effect being reported was after the first dose of Alec, administered soon after birth, which was not so. The Panel considered that the claim was misleading and a breach of Clause 7.2 was ruled.

The Panel noted that the claim was supported by data in babies of a gestational age of 23-29 weeks. Alec was for use in babies of 25-29 weeks. The Panel noted that the mailer did not refer to babies of less than 25 weeks and considered, therefore, that the claim did not constitute promotion outside the licence. No breach of Clause 3.2 was ruled.

Complaints received

Case AUTH/629/10/97	**21 October 1997**
Case AUTH/642/11/97	**12 November 1997**
Cases completed	**29 May 1998**

CASE AUTH/633/10/97 *NO BREACH OF THE CODE*

FORMER EMPLOYEE v ETHICAL GENERICS

Supply of Digenac

A representative who had been employed by Ethical Generics said that when he opened a new account with a dispensing surgery the company had supplied ten packs of Digenac whilst the account was being processed. The complainant alleged that no request was made in writing, the incentive was free goods if an account was opened and an order placed on the day, the product was not marked "medical sample not for resale" and there was no control over the distribution of samples.

The Panel did not consider that the packs had been supplied as samples. They had been supplied either as free goods or as an advanced supply for which the practice would eventually be invoiced. The Panel was not sure which was the case but considered that this was not relevant. If the Digenac had been supplied as free goods then, as the quantity provided was moderate, this was a trade practice relating to prices, margins and discounts which was outside the scope of the Code. If the Digenac had been an advanced supply for which the practice would eventually be invoiced, then this was a commercial deal which was not subject to the Code. No breach of the Code was ruled.

Upon appeal by the complainant, the Appeal Board considered that the packs of Digenac provided by the representative were not supplied as samples. The Appeal Board considered that whether the items were supplied as free goods or as advanced supply for which the practice would be invoiced was irrelevant. In either case the supply of the goods did not amount to a breach of the Code.

COMPLAINT

A former employee of Ethical Generics Ltd submitted a complaint about the supply of Digenac to a general practice.

The complainant explained that he had been employed as a generic sales manager with the task of opening as many accounts in dispensing surgeries as was possible and the incident in question occurred in one such surgery. Having seen the senior doctor and the practice dispenser on several occasions, the complainant had a final meeting to discuss prices during which the doctor checked Ethical Generic's four products with the products currently being prescribed. This occurred on 8 December 1996. Having reached agreement the doctor requested that the company supply samples to enable patients to be started on Digenac whilst the account was being processed. The complainant spoke to a secretary at his company who spoke to the sales manager who agreed to send a pack of ten packs for the surgery use if an account was opened with an order on that day. No request was made in writing and the incentive was free goods only if an account and an order was placed on that day. The free goods duly arrived the next day for the surgery and the complainant delivered them immediately. The account was opened in January 1997. None bore the required marking of "medical sample not for resale" nor was there any control over the distribution of the samples. The complainant alleged breaches of Clauses 17.3, 17.4, 17.9 and 18.1 of the Code.

The complainant stated that he could only act on head office instructions but was unhappy that the company appeared to be breaking regulations not only in this case but in some of the deals that had been conducted within the retail trade.

The complainant had been dismissed from the company for an unrelated matter and he said that he was currently taking the company to court.

RESPONSE

Ethical Generics explained that the complainant was employed as a representative. Each representative was supplied with the Code of Practice on commencement of employment and compliance with the Code was part of each representative's employment conditions. The company did not contest the fact that ten packs of Digenac were supplied to the surgery. However, it did not agree with the complainant's version of the sequence of events.

The company stated that the first it was aware of this event was when the complainant's administration of the surgery was discussed with him at a disciplinary hearing on 30 January 1997. At this meeting the complainant was

summarily dismissed for gross misconduct. The complainant informed the company that he had set up an account with the surgery and had issued the product to it. The complainant should not have issued free stock to the surgery as this was not a normal practice of the company. In doing so he was acting against the company's instructions and accordingly outside the course of his employment. However, the company was aware that it was possible, as the complainant's employer, to be deemed responsible for his actions.

The company's understanding was that the packs were presented to the surgery by the complainant in lieu of the surgery's first order and to allow it to start using the product whilst the administration of setting up a direct account was completed. In view of this the company did not believe that the product could be classified as samples and accordingly Clause 17 had no application. It followed that as the packs were in lieu of the first order, the supply of Digenac was neither a gift nor an inducement to prescribe. Accordingly the company submitted that the complainant had been acting outside the scope of his employment. Further, or in the alternative, the issue of the product to the surgery was free stock and not samples and consequently neither Clauses 17 nor 18 of the Code had any application.

PANEL RULING

The Panel noted that the supplementary information to Clause 17 of the Code defined a sample as a small supply of a medicine provided to members of the health professions in order that they might familiarise themselves with it and acquire experience in dealing with it. The supplementary information further stated that titration packs, free goods and bonus stock provided to pharmacists and others were not samples.

The Panel noted the company's submission that the representative was acting outside the company's instructions and accordingly outside the course of his employment. It noted that Clause 15.10 of the Code stated that companies were responsible for the activities of their representatives if these were within the scope of their employment even if they were acting contrary to the instructions which they had been given. The activities in question were within the scope of the representative's employment and Ethical Generics was therefore responsible for the conduct of the representative.

The Panel noted that the representative provided the dispensing practice with ten packs of Digenac following the opening of an account. This was, according to the company, in lieu of the surgery's first order.

The Panel did not consider that the packs of Digenac were supplied as samples. They were supplied as either free goods or advanced stock. The requirements of Clause 17 did not apply. The Panel therefore ruled no breach of Clauses 17.3, 17.4 or 17.9 of the Code.

The Panel noted that the supplementary information to Clause 18.1 "Terms of Trade" stated that measures or trade practices relating to prices, margins and discounts which were in existence in the pharmaceutical industry on 1 January 1993 were outside the scope of the Code and excluded from the provisions of Clause 18.1. The Panel considered that it was arguable as to whether the provision of free goods was a matter relating to "prices, margins and discounts". It was certainly an established practice to provide a limited supply of free goods in particular circumstances. The view of the Panel was that the provision of free goods in moderation was exempt from the Code as being an established trade practice related to prices, margins and discounts.

The Panel was unsure whether the ten packs of Digenac had been supplied as free goods or as an advanced supply for which the practice would eventually be invoiced, though the complainant's comments suggested that the former was the case. The Panel considered however that this was not relevant. If the Digenac had been supplied as free goods then, as the quantity provided was moderate, this was a trade practice relating to prices, margins and discounts which was outside the scope of the Code. If the Digenac had been an advanced supply for which the practice would eventually be invoiced, then this was a commercial deal which was not subject to the Code. The Panel therefore ruled no breach of Clause 18.1 of the Code.

APPEAL BY THE COMPLAINANT

The complainant said that he would like to point out several differences between the response to the Authority's investigation and the facts as they were.

The company response was that it only knew of the surgery event when discussed at a disciplinary hearing on 30 January 1997. The date on the application form from the surgery proved that the company was well aware of the issue from 8 December 1996. The complainant did not have any product to give the surgery. The request for a pack of samples was from the surgery not the complainant. If indeed the product the company supplied was in lieu of the first order then the proof would be that the surgery was invoiced for the product, which it was not.

Possibly the most important point was that the response from the company made it look as if the complainant was dismissed as a result of this issue. The complainant provided details of the reasons for his dismissal.

RESPONSE FROM ETHICAL GENERICS

The issues raised by the complainant in his letter of appeal seemed to Ethical Generics to focus upon differences of interpretation between the company's account of certain details surrounding this case and the complainant's own account of those details without actually providing reasons as to why the complainant did not accept the Panel's ruling with respect to the alleged breaches of Clauses 17 and 18 of the Code. The principal issues in this appeal were firstly whether the Digenac XL supplied by Ethical Generics was a sample within the meaning of Clause 17 of the Code and secondly whether the supply constituted any form of inducement to the doctor to prescribe, supply, administer or buy any medicine. It remained Ethical Generic's firm position that the Digenac provided to the surgery was not a sample, nor was it offered as an inducement.

Alleged breach of Clauses 17.3, 17.4 and 17.9

The definition of sample in the Supplementary Information to Clause 17 clearly stated in the first paragraph that the purpose of providing samples was to enable health professionals to familiarise themselves with the product and acquire experience in dealing with it. The second paragraph of the definition went on to state that free goods and bonus stock provided to pharmacists and others were not samples. With respect to the second paragraph of the definition Ethical Generics had already explained, and the Panel had accepted, that the Digenac provided to the surgery was provision of stock and could not therefore by definition be a sample. This finding was consistent with other recent cases concerning the supply of products as initial free stock (in particular Case AUTH/311/6/95).

With respect to the first paragraph of the definition, Ethical Generics believed it was relevant to mention that its business was concerned exclusively with the supply of generic medicines which, by their very nature, contained active ingredients which doctors were generally entirely familiar with since they would normally be changing from prescribing/dispensing a well known branded product to a generic. At this stage the doctor would usually have prescribed branded versions or even other generic versions of the product for many years. Accordingly, doctors did not generally require samples of generic medicines for familiarisation purposes. Indeed, in this particular case it was clear from the complainant's letter to the Authority that the product was required for treatment of patients and not for familiarisation purposes;

".... the doctor requested that the company supply samples to enable patients to be started on our generic ...."

In summary, there was scant demand for samples in a generics business which was why Ethical Generics did not now, and had never in the past, produced sample packs, and its account managers were perfectly aware of this fact.

Alleged breach of Clause 18.1

The stock provided to the surgery was not provided as an inducement to the doctor concerned to purchase or prescribe the company's products. It was Ethical Generics' understanding that the product was provided as initial stock to the doctor once the doctor had made the decision to stock Digenac. This understanding was consistent with the complainant's letter to the Authority. In any event, the supply of the product fell within the meaning of the terms of trade exemption to Clause 18.1 At the relevant time this exemption provided that;

"measures or trade practices relating to prices, margins and discounts which were in existence in the pharmaceutical industry on 1 January 1993 are outside the scope of the Code and are excluded from the provisions of this clause".

It was clear following the Panel's and the Board's consideration of this exemption in Case AUTH/421/4/96 that reasonable trade practices which had been used prior to January 1993 would be exempt from the Code. Discounting by providing free stock was a well recognised and long established trade practice and in this particular case the quantity of product which was provided (ten packs worth £30) was significantly less than the 30 packs deemed acceptable in Case AUTH/311/6/95 and in Ethical Generics' view it was sufficiently modest to be "reasonable".

Notwithstanding that a number of the matters raised by the complainant in his appeal did not appear to be directly relevant to the subject matter of the appeal, Ethical Generics wished to take the opportunity to comment on the points raised since it believed the information provided misled as to a number of the background facts.

Date at which Ethical Generics became aware of Digenac supply to the surgery

The complainant alleged that the company was aware of the events relating to the surgery from 8 December 1996 since this was the date on the surgery's account application form. The account application forms were dated 8 December 1996 but the complainant did not provide Ethical Generics with those forms until the disciplinary hearing on 30 January 1997. Ethical Generics did not dispute that the complainant made a telephone request to the company around the time of the first week in December 1996 to request ten packs of Digenac and the product was subsequently dispatched to the complainant. However, Ethical Generics did not agree with the complainant that the meeting at the surgery and subsequent telephone call to the company took place on 8 December 1996, since this was a Sunday. Moreover, when the complainant requested the product the order was not stated to be for a named customer and Ethical Generics did not know that the complainant had provided the product to the surgery until he informed the company of this fact at the disciplinary meeting on 30 January 1997. A detailed chronology setting out the sequence of events was provided.

Product in lieu of first order

Ethical Generics' response to the Panel stated that the product supplied was provided either in lieu of the surgery's first order, or as free stock. The company's practice was to invoice customers for stock and, in line with accepted trade practice, discounts to customers would normally be handled by, for example, supplying 11 packs but invoicing the customer for ten packs. However, the account managers did have a discretion to provide customers with a small amount of free stock where they believed this was appropriate. In this case, had the complainant handled the opening of the surgery account in a timely manager the surgery would have been invoiced for the stock. However, since almost eight weeks had elapsed between receipt of the product by the surgery and the complainant advising the company that he had in fact provided the surgery with the stock, the company took the decision not to invoice the surgery, but rather to regard the supply as initial free stock.

Complainant's dismissal

Ethical Generics agreed that the complainant was not dismissed solely over his handling of the surgery account.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant said that the only comments he would make relating to the response from Ethical Generics were the ones previously supplied. However supplying ten packs of a product would have to be quantified as to who they were for, and why, as otherwise there would be no control.

Furthermore the company had stated that the paperwork did not arrive till late and they already know that this was because the bank account number was missed off the application form and the secretary had difficulty in finding the correct number on the correct account. Add to that delay the Christmas holidays for the company, plus meetings and then the doctors' time schedule and four weeks were lost easily.

APPEAL BOARD RULING

The Appeal Board considered that the packs of Digenac provided by the representative were not supplied as samples. The Appeal Board upheld the Panel's ruling of no breach of Clauses 17.3, 17.4 and 17.9 of the Code.

The Appeal Board considered that whether the items were supplied as free goods or as advanced supply for which the practice would be invoiced was irrelevant. In either case the supply of the goods did not amount to a breach of Clause 18.1 of the Code. The Appeal Board upheld the Panel's ruling of no breach of Clause 18.1.

The appeal therefore failed.

Complaint received **28 October 1997**

Case completed **18 March 1998**

CASE AUTH/636/11/97

HOSPITAL PHARMACIST v SCHWARZ PHARMA

Distribution of Tylex packs

The clinical director of pharmacy services at a Trust complained about the distribution of samples of Tylex capsules and tablets by Schwarz Pharma at a seminar at which the delegates had included nurses, pharmacists, general management and administrative staff as well as doctors. The Code allowed samples to be provided only in response to signed requests from healthcare professionals.

The Panel did not accept Schwarz's contention that the packs were not samples but were starter packs for use in instances where there would be a delay in filling a prescription. The Panel recognised that the boundary between starter packs and samples could be difficult to define. It did not depend merely on the labelling of the packs. The context in which the packs were distributed and to whom was more important. The packs of Tylex capsules were labelled as starter packs. There was no such labelling on the tablet packs. Notwithstanding the labelling of the capsules, the Panel considered that the packs had been distributed with the intention that doctors would try the product rather than use it when there might be a delay in filling a prescription. The packs had been used as samples and as they were not labelled as such a breach of the Code was ruled. There was no evidence that packs had been provided other than to health professionals and Schwarz had obtained signed and dated requests. No breach was ruled in that regard.

Upon appeal by both parties, the Appeal Board noted that there was no requirement to label starter packs. There was some confusion as to whether the packs had been distributed as starter packs or as samples. The packs of capsules were labelled as starter packs but there was no such labelling on the tablets. The signed request forms obtained by Schwarz were headed "Schwarz Pharma Sample Request". The Appeal Board considered that the packs had been used as samples and not as starter packs and upheld the Panel's ruling that there had been a breach of the Code because they had not been labelled "free medical sample - not for resale" or words to that effect. The Appeal Board noted that there was no evidence that the Tylex samples had been provided to anyone who was not a health professional. The Panel's ruling of no breach in that regard was upheld. The Appeal Board considered that the provisions relating to starter packs should be clarified when the Code was next revised.

The clinical director of pharmacy services at a Trust complained about the distribution of Tylex samples by Schwarz Pharma Limited. The samples had been distributed at a sponsored evening seminar entitled "Day Surgery The Way Forward" which was aimed at surgeons, anaesthetists, managers and nurses. The complainant wrote his letter of complaint to Schwarz and sent a copy of it to the Authority.

COMPLAINT

The complainant said that a large number of packs of Tylex were distributed by Schwarz to visitors and staff at the day case seminar. The complainant confirmed that a member of the pharmacy staff who had attended the seminar had been given a pack of Tylex.

While the complainant appreciated that delegates attending the seminar included many members of the medical profession, he pointed out that there were also nurses, pharmacists, general management and administrative staff present. The complainant said that these latter groups of staff should not be exposed to the possibility that they might be in receipt of medical samples of prescription only medicines. The complainant drew attention to Clause 17.1 of the Code which specifically forbade this form of promotion, and Clause 17.3 which stipulated that samples might only be supplied in response to written requests which had been signed and dated by the healthcare professional making the request. The complainant questioned whether Schwarz was able to supply copies of such signed requests. The complainant said that the packs issued on the night were not actually labelled as medical samples, but in fact contained a patient information leaflet, implying that a professional consultation had taken place.

The complainant considered that it was very irresponsible of Schwarz to allow the distribution of sufficient

quantities of this product, which, if ingested accidentally or in ignorance, could lead to harm. The complainant drew attention to the potential toxicity associated with co-codamol products when administered inappropriately and without medical supervision.

The complainant was also concerned that Tylex was not the brand of co-codamol 30/500 either routinely stocked or currently preferred by the Trust. Such overt promotional activity as that which took place at the seminar without prior knowledge or approval did little to foster future collaborative relations between the Trust and Schwarz.

The complainant sent Schwarz the Trust's guidance for pharmaceutical representatives, and asked Schwarz to instruct its local staff to uphold this guidance at all times when visiting the Trust.

RESPONSE

Schwarz said that the representative concerned was asked to sponsor the PGEA, PREP and CME accredited seminar. This was agreed to on the reasonable assumption that the majority of attendees at such a meeting would be medically qualified, which was the case. Sponsorship involving the erection of a stand and distribution of promotional materials was agreed with the course organiser. The representative was also prudent enough to check that the distribution of starter packs in accordance with the ABPI guidelines was also acceptable, which it was.

Schwarz said that the packs issued at the meeting were not labelled as 'free medical samples' as they were starter packs intended for use in instances where there was an undesirable delay in filling a prescription. These were only issued to medically qualified doctors who were asked to sign and date a request form. These forms were not provided but the company offered to make them available for inspection if required. Schwarz said that it appeared that the date had been omitted from some, although this could be established from the code numbers and delegate list.

Schwarz said that the meeting was a busy one with over 200 delegates but every reasonable effort was made to comply with the Code and individual hospital requirements. If a non-medically qualified person did obtain a starter pack it would have been by devious means. Forty five starter packs of Tylex Capsules and Tylex Effervescent were distributed at the seminar. Packs of each were provided.

Schwarz said that there were two representatives managing the stand which was normal for a meeting of this type. Those requesting a starter pack were asked if they were medically qualified prior to completing a written request.

Schwarz considered that the question that must be answered here was not, was it possible for a non-medically qualified person to obtain a Tylex starter pack by devious means? But rather, was every reasonable effort made to comply with the Code and individual hospital requirements?

Having thoroughly investigated this incident, Schwarz considered that every reasonable effort was made on this occasion. The company had taken steps to remind all of its representatives of the strict procedure for the distribution of starter packs.

Schwarz denied a breach of Clause 17.

PANEL RULING

The Panel noted that Clause 17 of the Code provided for the distribution of samples and that reference to starter packs was made in its supplementary information. The supplementary information stated that both samples and starter packs were small supplies of a medicine. Samples were provided in order that health professionals might familiarise themselves with a medicine and acquire experience in dealing with it. Starter packs were designed to provide sufficient medicine for a doctor to initiate treatment in circumstances where a delay in filling a prescription would be undesirable. The Panel recognised that the boundary between starter packs and samples could be difficult to define but considered that it did not depend merely on the labelling of the packs. The context in which packs were distributed and to whom was more important. Packs could be labelled as starter packs but nonetheless be distributed in such a way as to effectively make them samples. If a clear distinction was not made between the provision of samples and the provision of starter packs, the effect would be to allow companies to avoid the restrictions in the Code on the provision of samples and this would not be acceptable under either the Code or the law.

The Panel considered that, by their nature, starter packs would usually be supplied to GPs. Recipients would generally, but not exclusively, already use the medicine in question, would want to be able to use it in emergency situations and would be given a number of small packs with which to initiate therapy at night or at weekends. In the Panel's view, starter packs were not appropriate for hospital doctors. Hospitals would have their own systems to ensure that there were no delays in meeting requirements whenever they arose.

The Panel noted that samples were provided in order that health professionals might familiarise themselves with a medicine and acquire experience in dealing with it. The number of samples which could be provided was limited as was their size. The Panel noted that samples could be provided to health professionals and were appropriate both for general practice and for hospital use (subject to individual hospital rules in this regard).

The Panel noted that the packs of Tylex distributed at the seminar contained either eight tablets or eight capsules. The packs of capsules were labelled "Starter Pack". There was no such labelling on the tablet packs. Despite the labelling of the capsule packs the Panel considered that both packs of Tylex had been distributed with the intention that doctors would try the product. The packs had not been distributed in the context of being provided for a general practitioner's bag and for use on night and weekend calls where there might be a delay in filling a prescription. The packs had been distributed from a promotional stand. In the Panel's view the Tylex packs had been used as samples and not starter packs. The Panel noted that the packs had not been labelled "free medical sample - not for resale" or words to that effect. A breach of Clause 17.5 of the Code was ruled.

The Panel noted that the packs of Tylex had only been given to health professionals as required by Clause 17.1 of the Code. The Panel noted that the complainant had stated that one of the pharmacy staff had been given a pack of Tylex. The Code did not prohibit the provision of samples to pharmacists as such people were within the definition of health professional. Although there was a possibility that individuals other than health professionals might have received packs there was no evidence that this had in fact happened. Schwarz had obtained signed and dated written requests as required by Clause 17.3 of the Code. The Panel therefore ruled no breach of Clauses 17.1 and 17.3 of the Code.

The Panel noted the complainant's comment that the packs included a patient information leaflet. The Panel considered that this was quite proper. Patient information leaflets which were enclosed in normal sales packs had also to be included in sample and starter packs.

During its consideration of this case the Panel expressed concern about the distribution of medicines at exhibitions and conferences. In the Panel's view there was the potential for a large number of packs to be distributed in a busy environment to attendees not known to representatives. Companies would be well advised to ensure that the distribution of medicines at such events was well controlled.

APPEAL BY SCHWARZ PHARMA

Schwarz said that it was the company's understanding that it had followed the Code to the letter, and that it was fully appreciative of the spirit of the Code and acted with this in mind at all times.

Tylex was undoubtedly the "type of medicine" for which starter packs were appropriate and the packs in question were "small packs designed" with this purpose in mind. Whilst the Panel's comments about the method of distribution were appropriate, it was Schwarz's understanding that these did not form part of the Code and could not be reasonably inferred from the Code. Thus Schwarz could not accept a breach of the Code and it appealed against such. Schwarz fully appreciated that this case had highlighted an area of the Code which was unclear and it would support steps to modify the Code to ensure that greater clarity with regard to the definition, use and distribution of starter packs resulted.

APPEAL BY THE COMPLAINANT

The complainant appealed the ruling that the breach of Clause 17.5 had been the only breach of Clause 17.

Firstly, it was freely admitted by staff attending the event that certain doctors were identified by the representative at the event and that they did sign for the Tylex samples they were given. It had not been the complainant's intention to lead the Panel to believe that all samples were handed out in contravention of Clause 17, but that in the crowded circumstances described, samples were openly available to non-medical staff, thus creating the breach.

The assumption by Schwarz that the majority of attendees at such a meeting would be doctors was shown not to be so reasonable after all. Analysis of the delegate list showed that only 84 medically qualified attendees registered for the event, compared with 242 others, ie only 26% of registered attendees were actually doctors.

Amongst the "others" were 56 managers and operating department practitioners from a variety of local hospitals and health authorities. Many of these managers were neither registered nurses nor pharmacists. The complainant pointed out that Clause 17.1 did not permit samples to be provided to administrative staff. It appeared to the complainant that neither Schwarz nor he could either prove or disprove that this did not happen, but as a result of the setting and the sheer numbers attending, a high degree of control and accountability would have been needed to prevent this.

The response from Schwarz to the complaint suggested that "If a non-medically qualified person did obtain a starter pack it would have been by devious means". In response to this statement the complainant made the following observations.

The question of "If ..." did not arise, as non-medical hospital staff freely admitted that the samples were openly on display and available for self-selection without any intervention, and so there was absolutely no doubt that Tylex samples were obtained in this manner.

Staff attending the event who were employed at the Trust were wearing identification badges clearly stating their job title and/or profession. Would they have done this if they intended to behave deviously? There should, therefore, have been no difficulty in identifying those non-medical staff visiting the trade stand. As stated earlier, it was a very busy event, and it might have been difficult for the representatives present to have exerted adequate control of those visiting the stand. As the samples were on open display, did, therefore, a breach of Clause 17.9 occur, which in turn may have inadvertently led to the breach of Clause 17.1?

The complainant failed to understand Schwarz's intent in suggesting that "devious means" would have been used to obtain Tylex samples. To employ devious means implied knowledge of the process to be avoided or circumvented. The contents of the Code were not well known by most hospital staff. The event organiser certainly admitted to the complainant ignorance of such details and did not understand the implications of the agreement to permit the distribution of promotional materials. In fact one nurse thought that the Tylex sample pack she picked up would have contained either a sewing kit or a highlighter pen - she was very surprised to find actual medicines instead.

The non-medical professional staff who obtained the samples worked daily in operating theatres, wards and pharmacies where they were responsible for ordering, storing and preparing large quantities of potent medicines, including controlled drugs. With that degree of access to such medicines, would they have had need to behave deviously at this seminar to obtain eight capsules of Tylex? Why, if they had obtained these capsules by devious means, would they freely and openly volunteer this information to senior hospital managers after the event? The complainant assured Schwarz that all hospital staff had, and were seen to uphold, their own codes of professional practice, and that these codes did not condone any form of "devious" behaviour whatsoever. Members of the Appeal Board would, of course, be very

familiar with these codes and would need no such assurance. The complainant invited Schwarz to submit the supporting evidence for this or, if unable to do so, then to withdraw it altogether.

In conclusion, the complainant said that he agreed and accepted there was a breach of Clause 17.5. He believed his statement had given further weight to the likelihood of a breach of Clause 17.1, no doubt as a result of Clause 17.9 being breached at the event. However, without detailed scrutiny of the delegate list, the signed requests in Schwarz's possession, and extensive staff interviews, the complainant doubted whether any one would ever know whether a serious breach of Clause 17.3 actually occurred.

RESPONSE FROM SCHWARZ PHARMA

Schwarz said that it realised it had caused offence by its choice of words and apologised for the ambiguity caused by the word "devious". There was no allegation, Schwarz merely intended to point out that if any starter packs had been obtained by non health professionals, it was not through accepted or approved procedures. If Schwarz had inadvertently offended, it was not its intention.

On reading the additional statement of the complainant, Schwarz agreed this situation was not ideal, but the facts to date had not demonstrated that a non health professional was provided with a Tylex starter pack or shown that starter packs were supplied without written requests. It would, therefore, seem just for the Panel's original ruling on Clauses 17.1 and 17.3 to stand.

The additional point that having starter packs on a display stand was a breach of Clause 17.9 was debatable. Providing no starter packs were removed without the agreement of the company representatives, there should be no problem. Schwarz would be making sure its field force continued to be extra vigilant on this front.

Schwarz believed every reasonable effort was made, both prior and during the meeting, to comply with the Code and with its spirit.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant said that the apology was very welcome and he accepted the context in which it had been offered. He had nothing to add to his previous comments.

FURTHER INFORMATION FROM SCHWARZ PHARMA

Schwarz provided copies of the signed written request forms to the Appeal Board. Each form was headed "Schwarz Pharma Sample Request".

APPEAL BOARD RULING

The Appeal Board noted that this was the first time it had considered a complaint which dealt with the differences between samples and starter packs. The Appeal Board noted that Clause 17 of the Code gave a clear description of what samples were together with how they should be labelled, distributed and accounted for. The Code itself did not define starter packs although an explanation was included in which the supplementary information stated that starter packs were small packs of medicines designed for a doctor to use to initiate treatment in such circumstances as a night call when there might otherwise be an undesirable delay in filling a prescription. The types of medicine for which starter packs was appropriate were limited. The supplementary information stated that starter packs were not classified as samples.

The Appeal Board agreed with Schwarz that the Code was unclear with regard to the definition and provision of starter packs. The provisions should be clarified the next time the Code was amended.

Turning to the case now before it the Appeal Board noted that there was some confusion as to whether the packs of Tylex had been distributed as samples or starter packs. The packs of capsules had been labelled "Starter Pack" although there was no such labelling on the tablet packs. There was no requirement in the Code for starter packs to be labelled as starter packs. Samples had to be clearly identified by their labelling. The packs of Tylex had been distributed following the receipt of a signed and dated request form which was a Code requirement for samples but not for starter packs. The Appeal Board noted that the request forms were headed "Schwarz Pharma Sample Request". The Appeal Board considered that notwithstanding the labelling of the capsule packs the packs had been used as samples and not as starter packs. The Appeal Board considered that this impression would be reinforced by the setting in which the packs were distributed. The packs had not been labelled "free medical sample - not for resale" or words to that effect. The Appeal Board upheld the Panel's ruling of a breach of Clause 17.5.

The respondent's appeal therefore failed.

The Appeal Board noted that there was no evidence that the Tylex samples had been provided to anyone who was not a health professional. The samples had been supplied in response to written requests which had been signed and dated. The Appeal Board therefore upheld the Panel's rulings of no breach of Clauses 17.1 and 17.3 of the Code.

The complainant's appeal was therefore unsuccessful.

During its consideration of this case the Appeal Board echoed the Panel's concerns regarding the need to ensure that the distribution of samples at exhibitions and conferences was well controlled.

Complaint received **3 November 1997**

Case completed **16 April 1998**

CASE AUTH/640/11/97

SMITHKLINE BEECHAM v ASTRA

Promotion of Colazide

SmithKline Beecham complained about a journal advertisement, two mailings and an information pack issued by Astra in relation to Colazide (balsalazide).

The claim "Sending more patients into remission than mesalazine" and other similar claims in the promotional materials were alleged by SmithKline Beecham to be unfair, unbalanced and misleading. SmithKline Beecham drew attention to the claim that "Colazide has been shown to send more ulcerative colitis patients into complete remission than mesalazine and also offers greater and faster symptom relief". The advertisement specifically identified the mesalazine preparation under comparison as pH(7)-dependent delayed release mesalazine, clearly suggesting that the comparator was SmithKline Beecham's product Asacol. SmithKline Beecham was aware of only two studies conducted to compare the efficacy of balsalazide and Asacol. One by Green *et al* found that balsalazide was statistically significantly superior to mesalazine in achieving both symptomatic and sigmoidoscopic remission of acute ulcerative colitis with significantly fewer patients reporting adverse events. Conversely Levine *et al* found no such differences between the products.

The Panel noted that the Green study concluded that balsalazide was more effective than mesalazine. The Levine study concluded that Colazide 6.75g/day was superior, though not statistically significantly different to Asacol in improving signs and symptoms. The Green study was on patients with moderate or severe ulcerative colitis whereas the Levine study was on patients with mild to moderate ulcerative colitis. Both products were indicated for mild to moderate ulcerative colitis. The Panel considered that the data showing an advantage for Colazide over mesalazine in mild to moderate ulcerative colitis was limited and decided that the claim at issue was not a balanced reflection of all the available data. A breach of the Code was ruled. Other similar claims in the materials were also ruled in breach.

Upon appeal by Astra, the Appeal Board noted that it had been supplied with further information about inclusion and exclusion criteria in the Green study. The Appeal Board noted that although the Green study included patients with symptoms described as moderate to severe this did not directly equate to disease state. The Appeal Board was satisfied that the study had excluded patients with severe disease and had thus been carried out on patients with mild to moderate disease. The Appeal Board considered that on balance the claims were a balanced reflection of the data and no breach was ruled. The appeal was accordingly successful.

SmithKline Beecham further alleged that the claims "Better tolerated than mesalazine" and that "... significantly fewer patients (48%) reported adverse events compared to the mesalazine group (71%) (p=0.024)" were unfair, unbalanced and misleading in breach of the Code. The claims were not supported by the data. For example, Levine reported no statistically significant differences between balsalazide and mesalazine in this regard.

The Panel noted that the Green study concluded that balsalazide was associated with a better adverse reaction profile and that the Levine study stated that no differences were observed. The Panel considered that the claims that Colazide was better tolerated than mesalazine based solely on the Green data were not a balanced reflection of all the evidence and a breach of the Code was ruled.

SmithKline Beecham Pharmaceuticals UK complained about the advertising of Colazide (balsalazide) by Astra Pharmaceuticals Ltd. The promotional materials at issue were an advertisement (COL/ADV2382) which had appeared in a number of journals including Pharmacy in Practice, October 1997, two mailers (COL/MLR2371 and COL/MLR2372) which had been sent to hospital doctors, GPs and retail pharmacists and an information pack (2354) provided to healthcare professionals by Astra representatives and by the medical information department. SmithKline Beecham was concerned about claims made in the materials comparing balsalazide and mesalazine. The materials referred to pH(7)-dependent delayed release mesalazine which was SmithKline Beecham's product Asacol.

1 Claim "Sending more colitis patients into remission than mesalazine"

COMPLAINT

SmithKline Beecham drew attention to a claim in the journal advertisement that "Colazide has been shown to send more ulcerative colitis patients into complete remission than mesalazine and also offers greater and faster symptom relief". The claim was referenced to a published abstract by Green *et al* (1996). SmithKline Beecham pointed out that the advertisement specifically identified the mesalazine preparation under comparison as pH(7)-dependent delayed release mesalazine, clearly suggesting that balsalazide demonstrated superior efficacy to Asacol.

SmithKline Beecham was aware of only two studies conducted to compare the efficacy of balsalazide and Asacol. The first was presented by Green *et al* at a meeting of the British Society of Gastroenterology in 1996 and again at the 97th annual meeting of the American Gastroenterological Association (AGA) in Washington and formed the basis for Astra's claims. The Green study found that balsalazide was statistically significantly superior to mesalazine in achieving both symptomatic and sigmoidoscopic remission of acute ulcerative colitis with significantly fewer patients reporting adverse events.

SmithKline Beecham referred to a second study presented at the recent meeting of the AGA, a study by Levine *et al* (1997), which found no such differences between the products. The Levine study was of a similar size to the study by Green. Patients were again evenly matched and they received Asacol and balsalazide at standard doses. However by the end of the study (week 8) Levine *et al* found no statistically significant differences between Asacol 2.4g/day and balsalazide 6.75g/day with regard to efficacy. During the entire trial a statistically significant

improvement in favour of balsalazide was observed in only one of a number of measures, this being sigmoidoscopic appearance at week 2. This difference disappeared at the end of the trial. The study was sponsored by Salix which would be marketing balsalazide in the US.

SmithKline Beecham alleged that, in the absence of any additional data to confirm the findings of Green *et al*, the claims presented were unfair, unbalanced and misleading in breach of Clause 7.2 of the Code.

RESPONSE

Astra was only aware of two studies which had directly compared the efficacy and tolerability of balsalazide (6.75g/day) and mesalazine (2.4g/day), these being Green *et al* (sponsored by Astra) and Levine *et al* (sponsored by Salix). There were key differences in the end points and information available from the two studies. This had a bearing on how the results should be assessed and compared.

Astra confirmed that data from Green *et al* had been presented at a meeting of the British Society of Gastroenterology and at the AGA meeting in Washington. The manuscript had been accepted for publication in Gastroenterology and was provided in confidence to the Panel and should not be forwarded to the complainant as it was pre-publication. Data on file, based on some of the data from the manuscript, had been used by Astra to support the claims made in the Colazide promotional material.

Astra pointed out that data from the Levine study were also presented at the AGA meeting but were available in preliminary abstract form only and publication status was not known.

Green *et al* compared Colazide (6.75g/day) with mesalazine (2.4g/day) in a UK multi-centred randomised double-blind trial in 99 patients with symptomatic ulcerative colitis. Treatment was for four to twelve weeks as needed and patients left the study after 4 or 8 weeks if they had achieved complete remission. The number of patients in complete remission was assessed after four, eight and twelve weeks. Complete remission was clearly defined as none/mild symptoms and sigmoidoscopy grade 0 (normal) or 1 with no steroid use in the previous four days. Green *et al* showed that Colazide was more effective than mesalazine in producing both symptomatic and sigmoidoscopic remission of active ulcerative colitis. The number of patients who achieved complete remission was significantly higher in the Colazide group than in the mesalazine group at 4 ($p<0.01$), 8 ($p<0.005$) and 12 ($p<0.05$) weeks. The proportion of patients who achieved complete remission after 12 weeks' treatment with mesalazine (37%) was similar to that achieved after only 4 weeks treatment with Colazide (38%). After 12 weeks, 62% of the Colazide group were in complete remission.

Astra submitted that a greater proportion of patients achieved symptomatic remission (none/mild symptoms) after Colazide compared to mesalazine. A significant difference between the two treatments was found after 2 weeks of treatment. After 12 weeks the proportion in symptomatic remission for Colazide compared with mesalazine was 88% versus 57% ($p<0.001$). Analysis of diary card data showed that symptom relief occurred more rapidly with Colazide. The median time taken to achieve the first symptom free day was ten days with Colazide and 25 days with mesalazine ($p<0.005$). Patients in the Colazide group experienced more days with complete symptom relief (using no steroid) during the first 4 weeks of treatment, compared with the mesalazine group ($p<0.01$).

Astra stated that the Levine study also compared Colazide 6.75g/day with mesalazine 2.4g/day in two out of three arms of a US multicentre study in a total of 154 patients with mild-moderate active ulcerative colitis. After two weeks' treatment significantly more patients showed sigmoidoscopic improvement in the Colazide group compared with the mesalazine group (56% versus 32%, $p=0.016$). At the end of the 8 week study there were no significant differences between Colazide and mesalazine. Complete remission (not defined in the abstract) was 23% versus 19% respectively. The proportions of patients showing an improvement in the Colazide group versus mesalazine group respectively were 79% versus 61% for sigmoidoscopic improvement, 74% versus 62% for physicians' global assessment, 65% versus 53% for rectal bleeding, 59% versus 58% for stool frequency, 71% versus 61% for patient functional assessment, and 41% versus 44% for pain. The authors concluded that Colazide was superior although not statistically significantly different from the mesalazine preparation in improving signs and symptoms of ulcerative colitis at 8 weeks.

Astra submitted that the Green *et al* study was conducted to stringent study design where the primary efficacy endpoint of complete remission comprised of 3 factors: none or mild symptoms; sigmoidoscopy grade 0/1; no use of rectal steroid foam within previous 4 days. The definition of remission varied in therapeutic studies in acute ulcerative colitis; improvement in clinical symptoms might be reported separately to sigmoidoscopic findings. The Green *et al* study specifically included a composite primary efficacy endpoint as a stringent composite assessment of the two products. In contrast, the definition of complete remission in the Levine study was not stated in the abstract.

The Green *et al* study consisted of a 12 week follow-up period (consistent with the Colazide licence) compared with an 8 week follow-up in the Levine *et al* study. Astra had looked at studies in the published literature which assessed the same doses of either balsalazide or mesalazine as used in the Green *et al* study. Whilst there was variability in efficacy endpoints used in these studies, the efficacy outcomes of the Green *et al* study were consistent with those seen for balsalazide and mesalazine respectively.

The Green *et al* study also included the efficacy endpoint of time to first symptom-free day which did not feature in the results of the Levine *et al* study. Furthermore, Astra was not aware that this endpoint had been used in studies of pH(7)-dependent delayed release mesalazine and had not received any information to the contrary from SmithKline Beecham.

In summary, Astra stated that there were two head to head studies which compared Colazide and pH(7)-dependent delayed release mesalazine. Full information was available on the Green *et al* study which used a

stringent composite definition of complete remission as a primary endpoint, in contrast to the Levine *et al* study, which was available in abstract form only, with an unknown definition of remission. The Green *et al* study demonstrated that significantly more patients achieved complete remission in the Colazide group at 4, 8 and 12 weeks; the Levine *et al* study reported that Colazide was superior although not statistically different from mesalazine in improving signs and symptoms at 8 weeks. Green *et al* also demonstrated significantly faster symptom relief in the Colazide group; this parameter was not assessed in the Levine *et al* study.

On this basis, Astra submitted that the claim "Colazide has been shown to send more ulcerative colitis patients into complete remission than mesalazine and also offers greater and faster symptom relief" was balanced and fair, based on available data, and represented the outcome of a rigorous assessment of Colazide compared with mesalazine.

PANEL RULING

The Panel noted that both Colazide and Asacol were indicated for the treatment of mild to moderate active ulcerative colitis. The Green *et al* study compared balsalazide and pH(7)-dependent delayed release mesalazine in acute moderate/severe ulcerative colitis. The patients (101 total, 99 evaluable) with grade 2, 3 or 4 sigmoidoscopically verified, symptomatic (moderate 69% or severe 31%) ulcerative colitis were randomised, double blind, to receive balsalazide 6.75g/day (n=50) or mesalazine 2.4g/day (n=49) for 4, 8 or 12 weeks as necessary. The Panel noted the study concluded that balsalazide was more effective than mesalazine in achieving both symptomatic and sigmoidoscopic remission of acute ulcerative colitis and was associated with a better adverse event profile.

The Panel noted the Levine *et al* study had been carried out on 154 patients with mild to moderate active ulcerative colitis. The aim of the 8 week study was to determine the dose response and relative efficacy of Colazide and Asacol. The study showed a statistically significant difference at 2 weeks in favour of Colazide. The study concluded that Colazide 6.75g/day was superior, though not statistically significantly different to Asacol in improving signs and symptoms of ulcerative colitis.

The Panel noted that there were only two studies directly comparing Colazide with pH(7)-dependent delayed release mesalazine. The Green study had shown statistically significant differences between the products and the Levine study had shown advantages for Colazide for a number of parameters measured.

The Panel noted that the Green study was on patients with moderate or severe ulcerative colitis whereas the Levine study was on patients with mild to moderate ulcerative colitis. Colazide and Asacol were both indicated for use in mild to moderate ulcerative colitis. The Panel considered that the data showing an advantage for Colazide over mesalazine in mild to moderate ulcerative colitis was limited and decided that the claim at issue was not a balanced reflection of all the available data. The Panel therefore ruled a breach of Clause 7.2 of the Code.

APPEAL BY ASTRA

Astra pointed out that the Panel had made its rulings based on the assumption that the Green study was on patients with moderate or severe ulcerative colitis whereas the Levine study was on patients with mild to moderate ulcerative colitis. Colazide and Asacol were both indicated for use in mild to moderate ulcerative colitis. The Panel considered that the data showing an advantage for Colazide over mesalazine in mild to moderate ulcerative colitis was limited and decided that the claims at issue were not a balanced reflection of all the available data. A breach of Clause 7.2 was therefore ruled.

Astra denied a breach of Clause 7.2 on the basis that the Green study was on patients with mild to moderate ulcerative colitis and excluded patients with severe ulcerative colitis. The data showing an advantage for Colazide over mesalazine in mild to moderate ulcerative colitis were therefore not limited and hence there had been a balanced reflection of all the available data.

In the Green study, 101 patients entered and the results of 99 with sigmoidoscopically and histologically confirmed mild to moderate ulcerative colitis were analysed. Patients with moderate to severe symptoms were included: 'moderate' = occasional interference with normal activities, 'severe' = frequent interference with normal activities. Patients' rating of severity of symptoms was subjective and based on quality of life; this was very different from the assessment of overall clinical severity of disease.

Whilst the Green study manuscript did not specifically state that the patients had mild to moderate ulcerative colitis, this was evident from the patient exclusion criteria cited.

For clarification, the specific inclusion and exclusion criteria which defined the severity of ulcerative colitis in the study population were:

Inclusion criteria

- sigmoidoscopically verified, grade 2-4 ulcerative colitis (grade 0 = normal, vascular pattern clearly visible (excluded at entry); grade 1 = erythema with loss of vascular pattern (excluded at entry); grade 2 = erythema with loss of vascular pattern plus contact bleeding; grade 3 = erythema with loss of vascular pattern plus spontaneous bleeding; grade 4 = erythema with loss of vascular pattern plus frank ulceration) which was verified no more than 3 days before initiation of therapy and extended >12cm beyond the anal margin;
- symptomatic (moderate or severe on patients' assessment) ulcerative colitis.

Exclusion criteria

- use of oral steroids or iv steroids, within 30 days before trial entry;
- a daily requirement for rectal steroids to maintain remission, prior to current relapse, or use of rectal steroids outside the product licence within 14 days before trial entry;
- use of immunosuppressive agents, eg azathioprine; cyclosporin and methotrexate within 3 months before trial entry;

- introduction or increase in dose of 5-ASA releasing compounds, eg sulphasalazine, olsalazine, mesalazine and balsalazide, or their regular use within 14 days before the trial at doses from which greater than 1.2g/day of 5-ASA is available;
- use of antibiotics for reasons related to the primary diagnosis or for other GI-related conditions within 14 days before trial entry;
- co-existing Crohn's disease or idiopathic proctitis;
- current complications of ulcerative colitis requiring iv steroids and/or oral steroids, eg passage of more than 6 bloody stools daily associated with any one of the following signs of systemic disturbance: temperature >37.5°C, pulse >100/min, haemoglobin <10g/dl or serum albumin <35g/dl.

Truelove's criteria were an accepted method of assessing the clinical severity of ulcerative colitis:

Severe - Severe diarrhoea (six or more motions a day) with macroscopic blood in stools. Fever (mean evening temperature more than 99.5°F (37.5°C), or a temperature of 100°F (37.8°C) or more on at least two days out of four). Tachycardia (mean pulse rate more than 90 per minute). Anaemia (haemoglobin 75% or less - allowance made for recent transfusion). ESR much raised (more than 30mm in one hour).

Mild - Mild diarrhoea (four or less motions a day) with no more than small amounts of macroscopic blood in stools. No fever. No tachycardia. Anaemia not severe. ESR not raised above 30mm in one hour.

Moderately severe - Intermediate between severe and mild.

Based on Truelove's criteria, patients with severe ulcerative colitis were excluded from the Green study. Confirmation of the patient population was provided in a letter from Dr Green, the principal investigator for the study, who stated that only patients with moderate and severe symptoms entered the study. Patients with mild symptoms (aware of symptoms, easily tolerated with no interference with normal activities) were excluded. Patients required to have an abnormal sigmoidoscopy. Dr Green also pointed out that there was no clear correlation between symptoms and overall severity of illness in ulcerative colitis. Moderate to severe symptoms did not equate to moderate/severe disease or illness level.

The Green paper had been published in Gastroenterology.

Astra also pointed out that the Green study was a pivotal study for obtaining the licence for Colazide for the treatment of mild to moderate ulcerative colitis.

Astra believed that the Panel had misinterpreted the severity of ulcerative colitis included in the Green study and it therefore appealed against the ruling of breaches of Clause 7.2 in points 1, 2 and 4.

APPEAL BOARD RULING

The Appeal Board noted that, with regard to the Green study, it had been supplied with additional information about the inclusion and exclusion criteria to that which had been supplied to the Panel. The Appeal Board did not consider that the Panel's decision had been unreasonable in the circumstances. It was clear that although the study included patients with symptoms described as moderate to severe this did not directly equate to disease state. The Appeal Board was satisfied that the Green study had excluded patients with severe disease and had thus been carried out on patients with mild to moderate disease.

The Appeal Board noted that the comparative claims were based on two studies, the Green study which showed statistically significant advantages for Colazide and the Levine study which had shown trends in favour of Colazide although statistical significance had not been reached. The Appeal Board noted that the Green study had been published while the Levine study was only available as an abstract from a scientific congress. The Appeal Board considered that on balance the claim "Sending more colitis patients into remission than mesalazine" was a balanced reflection of the data. No breach of Clause 7.2 of the Code was ruled.

The appeal was therefore successful.

2 Claims "Sending more patients into symptomatic remission than mesalazine"

These claims appeared on the promotional mailings (COL/MLR2371 & 2372).

COMPLAINT

SmithKline Beecham drew attention to the claim "Sending more colitis patients into remission than mesalazine" which appeared in the two promotional mailers. The claim was referenced to the Green study and to data on file which provided further information from the Green study not presented in the abstract. SmithKline Beecham alleged that for the reasons described in point 1 above the claim "Sending more colitis patients into remission than mesalazine" and other statements claiming superior efficacy for balsalazide were unfair, unbalanced and misleading. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Astra submitted its response in point 1 applied to the mailings at issue.

PANEL RULING

The Panel considered that its ruling in point 1 similarly applied to the promotional mailings. Each was ruled in breach of Clause 7.2 of the Code.

APPEAL BY ASTRA

Astra submitted that its appeal in point 1 applied to the mailings at issue.

APPEAL BOARD RULING

The Appeal Board considered that its ruling in point 1 similarly applied to the promotional mailings and the appeal was therefore successful.

3 Claim "Better tolerated than mesalazine"

COMPLAINT

SmithKline Beecham pointed out that both promotional mailers included the claim "Better tolerated than mesalazine" and that "... significantly fewer patients (48%) reported adverse events compared to the mesalazine group (71%) (p=0.024)". SmithKline Beecham alleged that the claims were not supported by the body of data available. For example Levine reported no statistically significant differences between Asacol 2.4g/day and balsalazide 6.75g/day in terms of the number of patients reporting adverse events, the distribution of adverse events or their severity. In addition Giaffer *et al* (1992) compared the tolerability of Asacol, olsalazine and balsalazide in patients who could not tolerate or who were allergic to sulphasalazine. Similar tolerability for all products was reported. SmithKline Beecham alleged that any claims relating to superior tolerability were therefore unfair, unbalanced and misleading. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Astra pointed out that there were only three references in the published literature relating to direct clinical safety comparisons of Colazide and mesalazine, Levine *et al* reported that there were no differences in the number of patients reporting adverse events or their distribution and severity but no further details were available in the abstract. Green *et al* reported that in the Colazide group significantly fewer patients (48%) reported adverse events compared to the mesalazine group (71%) p=0.024 and that the total number of adverse events with Colazide was less than half that recorded for mesalazine (46 versus 97).

Giaffer *et al* reported similar tolerability of balsalazide, olsalazine and mesalazine in a subset of patients who could not tolerate sulphasalazine, but it should be noted that this study used lower doses of both balsalazide and mesalazine than was recommended in their SPCs for acute disease and lower doses than those used in the Green *et al* and Levine *et al* studies. It did not necessarily follow that similar tolerability would be seen at the higher doses of balsalazide and mesalazine.

In summary, there were differing reports of the tolerability of Colazide and mesalazine when compared directly at the usual recommended doses for acute ulcerative colitis. This was based on detailed information from the Green *et al* study and summary information from the Levine *et al* study. Astra acknowledged that this could be made clearer in the Colazide promotional materials but this did not prevent the company from describing the tolerability results in the Green *et al* study.

PANEL RULING

The Panel noted the results of the Green *et al* and Levine *et al* studies. The Green *et al* study stated that all four serious adverse events (complications of ulcerative colitis) occurred in the mesalazine group and fewer patients in the balsalazide group reported adverse events (48% vs 71%, p<0.05). The study concluded that balsalazide was associated with a better adverse event profile. The Levine study stated that no differences were observed among treatment groups in the number of patients reporting adverse events or their distribution and severity.

The Panel considered that the claims that Colazide was better tolerated than mesalazine based solely only on the Green data were not a balanced reflection of all the evidence. The Panel therefore ruled a breach of Clause 7.2 of the Code.

4 Colazide Information Pack

COMPLAINT

SmithKline Beecham assumed that as the Information Pack included prescribing information and did not carry information relating to a particular customer it had been prepared as a promotional item rather than as a response to a direct request from a healthcare professional for information. As a detailed summary of information which clinicians or pharmacists were likely to retain as a reference document to support future prescribing of the product, it was particularly disturbing to SmithKline Beecham to see information represented in a misleading and unbalanced manner. Misleading claims relating to the superior efficacy and tolerability of balsalazide over Asacol, similar to those mentioned above, were given in Section 1 (Summary) and Section 2 (Tolerability). As previously alleged such claims could not be supported by the body of evidence available and were therefore in breach of Clause 7.2 of the Code.

SmithKline Beecham also drew attention to Section 5.1 (Comparison with a mesalazine preparation) which clearly demonstrated the unbalanced nature of the information that Astra was presenting to healthcare professionals. This section provided 5 paragraphs of detailed information relating to the Green study with only one sentence devoted to the study by Levine. That sentence read "Significantly more patients showed sigmoidoscopic improvement after two weeks treatment with Colazide" and failed to represent the full results of the study, namely that there were no significant differences between Asacol and balsalazide at the end of the study period with regard to efficacy or tolerability.

RESPONSE

Astra submitted that as the Information Pack contained similar efficacy and tolerability claims to the journal advertisement and the mailers its comments were the same as above. It should be noted that the Information Pack contained a summary of information from Green *et al*, Levine *et al* and Giaffer *et al* in addition to other references. This item was prepared by the medical information department.

Astra had reviewed the Information Pack and shared the concern that it should have contained more information on the Levine *et al* study. Astra placed significant emphasis on the quality of its medical information service and immediate steps had been taken to thoroughly review and amend the Information Pack; the September 1997 version had been withdrawn and replaced by an updated version. SmithKline Beecham was informed on 5 November 1997 that Astra had taken immediate steps to address this matter.

PANEL RULING

The Panel noted that Section 6 of the Information Pack was headed "Tolerability" and not Section 2 as stated by SmithKline Beecham. Section 2 was headed "Introduction".

The Panel noted that the allegations made about the Information Pack were similar to those made above. The Panel noted that in the description of the study by Green *et al* no mention had been made of the fact that the patients treated were those with moderate to severe ulcerative colitis. Both Colazide and Asacol were indicated in mild to moderate active ulcerative colitis. It noted that Astra had withdrawn the Information Pack on 5 November.

The Panel considered that its rulings of a breach of Clause 7.2 in points 1 and 3 above also applied to the Information Pack. Breaches of Clause 7.2 of the Code were therefore ruled.

APPEAL BY ASTRA

Astra accepted the Panel's ruling of a breach of Clause 7.2 of the Code that claims that Colazide was better tolerated than mesalazine were not a balanced reflection of all the evidence as given in point 3 above.

Astra submitted that its appeal in point 1 above applied to the efficacy claims in the Colazide Information Pack.

APPEAL BOARD RULING

The Appeal Board considered that its ruling in point 1 similarly applied to the Colazide Information Pack and the appeal on this point was therefore successful.

Complaint received **10 November 1997**

Case completed **17 April 1998**

CASE AUTH/649/11/97

BOEHRINGER INGELHEIM v UCB PHARMA

Preservex advertisement

Boehringer Ingelheim complained about an advertisement for Preservex issued by UCB Pharma claiming that the strapline "A world of difference in the joint" which followed the claim "An exciting step in arthritis research and treatment" clearly implied some special and new effect in the joint of an arthritis sufferer when treated with Preservex compared with other non-steroidal anti-inflammatory drugs (NSAIDs). Boehringer Ingelheim alleged that the advertisement was misleading and implied special merit which had not been substantiated.

In the Panel's view the treatment of arthritis with NSAIDs was so well established that doctors reading the advertisement would assume that the claims were in comparison with other NSAIDs. Doctors would not assume that the claims related to the affects of Preservex versus no therapy. The Panel considered that the claims were exaggerated and implied a special merit for Preservex which could not be substantiated and ruled that the Code had been breached.

Upon appeal by UCB, the Appeal Board considered that the advertisement would be viewed against the background of current therapy for arthritis. The claims would be seen as implying a special merit for Preservex compared to existing therapy. They were exaggerated and implied a special merit which could not be substantiated. The Appeal Board upheld the Panel's ruling of a breach.

Boehringer Ingelheim Limited complained about an advertisement for Preservex (UCB-P-97-07) issued by UCB Pharma Limited. UCB, although not a member of the ABPI, had nevertheless agreed to abide by the Code.

The advertisement, which was headed "Welcome to the world of Preservex", referred to the product (aceclofenac) as "An exciting step in arthritis research and treatment". Underneath the Preservex logo was the strapline "A world of difference in the joint". The advertisement had appeared in a number of publications including the British Medical Journal, 1 November 1997.

COMPLAINT

Boehringer Ingelheim was concerned about the use of the strapline "A world of difference in the joint" following the claim "An exciting step in arthritis research and treatment". This strapline clearly implied some special and new effect in the joint of an arthritis sufferer when treated with Preservex compared with other non-steroidal anti-inflammatory drugs (NSAIDs).

Boehringer Ingelheim said that UCB's response when challenged was that it was perfectly reasonable to state that patients receiving Preservex would note an improvement in joint pain and mobility etc, associated with the above conditions compared to patients not receiving treatment. UCB had thus offered no evidence that Preservex was any different from other NSAIDs in its effect on the arthritic joint.

Boehringer Ingelheim alleged that the advertisement was misleading and implied that Preservex had some special merit in treating the arthritic joint which had not been substantiated in breach of Clause 7.8 of the Code.

RESPONSE

UCB stated that Preservex was for the relief of pain and inflammation in osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. The company considered that it was perfectly reasonable to state that Preservex would be of benefit to such patients with conditions which affected their joint regions, and the strapline "A world of difference in the joint" properly reflected this. UCB said

that if this strapline had been used by Boehringer Ingelheim for one of its NSAID products it was not one to which UCB would have objected as it could be used for any NSAID which effectively relieved pain and inflammation in the joint.

UCB noted that Boehringer Ingelheim additionally appeared to be concerned about the use of the claim "An exciting step in arthritis research and treatment". It was not clear whether Boehringer Ingelheim was concerned about this claim in isolation, or because it was directly linked to "A world of difference in the joint". If it was the latter then UCB noted that the claim and the strapline were clearly separated in the advertisement in terms of position, type size and colour.

UCB did not consider that the claim breached Clause 7.8 of the Code. This claim reflected the fact that much research work had been carried out into the mode of action of aceclofenac, eg its effect on glycosaminoglycan synthesis in osteoarthritic cartilage, its effects of synovial inflammatory factors, such as PGE_2 and interleukin - 1ß, which were known to play an important role in the degeneration of the joint articular tissues of patients with osteoarthritis. A review of some of this research was provided. UCB said that the review provided support for the company's belief that aceclofenac was of benefit to a patient's arthritic joint. Further articles in support of this position could be supplied.

UCB noted that Boehringer Ingelheim had said that it had offered no evidence that Preservex was any different from other NSAIDs in its effect on the arthritic joint. As the advertisement did not mention any other NSAID, the NSAID group as a whole, or indeed any other medication, UCB did not consider this was unreasonable as no claim of uniqueness or superiority was made or implied in the advertisement.

UCB said that before preparing this advertisement it was aware that, in the past, a number of companies which had made claims for superior efficacy or safety over other NSAIDs had been ruled in breach of the Code. UCB did not consider that its advertisement made or implied such a claim and in particular it did not consider that it breached Clause 7.8.

PANEL RULING

In the Panel's view the treatment of arthritis with NSAIDs was so well established that doctors reading the advertisement would assume that the claims being made for Preservex, "An exciting step in arthritis research and treatment" and "A world of difference in the joint", were in comparison to other NSAIDs. The Panel did not consider that when reading the advertisement doctors would assume that the claims related to the effects of Preservex versus no therapy.

The Panel considered that the claims were exaggerated and implied a special merit for Preservex versus other NSAIDs which could not be substantiated as alleged. A breach of Clause 7.8 was ruled.

APPEAL BY UCB PHARMA

UCB said that it was its firm belief that the advertisement did not contain any claim which was either exaggerated or which implied that Preservex had some special merit over other NSAIDs.

In its original communication to UCB dated 6 October 1997, Boehringer Ingelheim objected to the use of the phrase "A world of difference in the joint". UCB did not believe that within the advertisement this claim implied any special merit versus other NSAIDs.

In Boehringer Ingelheim's letter of complaint to the Authority there appeared to be some concern that the phrase "An exciting step in arthritis research and treatment" preceded the strapline "A world of difference in the joint". Boehringer Ingelheim's objection to the use of the phrase "An exciting step in arthritis research and treatment" was only brought to UCB's attention via the Authority. UCB pointed out that both phrases were quite clearly separated in the advertisement in terms of their position, font size, font colour and font case.

However for the sake of completeness UCB was quite happy to substantiate the use of the phrase "An exciting step in arthritis research and treatment", although it would emphasise once again that it did not believe that its use in the advertisement implied a special merit over other NSAIDs.

A world of difference in the joint

UCB said that it took over the responsibility for marketing Preservex from Bristol-Myers Squibb Pharmaceuticals Ltd in mid 1997. One of its first objectives was to increase the awareness amongst doctors of the product name Preservex and to associate it with the treatment of arthritis. At this stage of the campaign it was decided that it was too early to also try and introduce comparisons with other products. Therefore the first point which UCB stressed was that there was no statement within the advertisement which attempted to compare Preservex with other NSAIDs as was suggested by Boehringer Ingelheim in its complaint.

Within the advertisement itself the main visual item consisted of a representation of the bones of the human hand within which the joints were highlighted. Once again this was intended to associate the name Preservex with the treatment of arthritis. This was emphasised by the use of the phrase "A world of difference in the joint" underneath the name Preservex. It was UCB's contention that such a statement was perfectly reasonable for a product such as Preservex whose principal site of action was the joint. UCB believed it to be fanciful to try and suggest that such a phrase "clearly implies" a "special merit" for Preservex over other NSAIDs as nowhere in the advertisement was there a reference made to the comparative merits of Preservex versus any other NSAID. Obviously in order to obtain a marketing authorization data had to be submitted to the Medicines Control Agency which demonstrated that the product would be of clinical benefit to patients with osteoarthritis, using such endpoints as assessments of joint mobility, swelling and pain. UCB therefore believed it was perfectly reasonable to suggest that patients with arthritic joints were likely to experience significant improvement in joint pain, function and mobility and the phrase "A world of difference in the joint" properly reflected this fact. UCB believed that it was unreasonable for the Panel to imply that this statement was an obvious comparison to other NSAIDs when the

overall presentation of the advertisement was taken into context.

An exciting step in arthritis research and treatment

Clinical studies conducted with aceclofenac had shown that it was at least as effective as well established NSAIDs such as diclofenac, indomethacin, ketoprofen, naproxen, and tenoxicam in the treatment of osteoarthritis, rheumatoid arthritis and/or ankylosing spondylitis. However an emerging picture from such investigations was that aceclofenac had been consistently better tolerated. This was exemplified by the findings of a meta-analysis of the results of 13 studies comprising 3,574 patients (Peris *et al* 1996). UCB particularly wished to emphasise the quality of the inclusion criteria for the meta-analysis, ie only clinical trials of at least 3 months' duration which were conducted under double-blind, parallel and randomised conditions. The analysis concluded that there was a statistical significance in favour of aceclofenac over the comparator NSAIDs in terms of patient compliance (ie the probability of a patient completing a study protocol), global safety and withdrawals. In addition, fundamental research was also being carried out to investigate the effects of aceclofenac on the mechanisms underlying the arthritic process. As an example of such work two articles were supplied on the findings of research which had found that different NSAIDs might stimulate, inhibit or have no effect on glycosaminoglycan (GAG) synthesis in arthritic cartilage (Dingle (1996) and Dingle (1997)). It was found that aceclofenac belonged to a group of NSAIDs which appeared to stimulate GAG synthesis which in turn could facilitate the repair and synthesis of articular cartilage in osteoarthritis which could make aceclofenac suitable for use in the long term treatment of osteoarthritis.

In addition a paper was supplied describing an investigation which found that aceclofenac was a potent inhibitor of interleukin IL-1 release (Gonzalez (1994)). It was known that human cartilage GAG synthesis had been shown to be sensitive to inhibition by IL-1 therefore the modulation of such mechanisms by drug intervention, whilst also ensuring that the therapy itself did not add to the problem (by inhibiting GAG synthesis for example). UCB believed such lines of research added support to its statement that aceclofenac offered "An exciting step in arthritis research and treatment".

In summary UCB did not believe that the advertisement "clearly implies some special and new effect in the joint of an arthritis sufferer when treated with Preservex compared with other NSAIDs", or that "this advertisement is misleading", as alleged by Boehringer Ingelheim.

APPEAL BOARD RULING

The Appeal Board considered that the advertisement would be viewed against the background of current therapy for arthritis. The claims for Preservex "An exciting step in arthritis research and treatment" and "A world of difference in the joint" would be seen as implying a special merit for Preservex compared to existing therapy. The Appeal Board considered that such claims were exaggerated and implied a special merit for Preservex versus other NSAIDs which could not be substantiated. The Appeal Board upheld the Panel's ruling of a breach of Clause 7.8 of the Code.

The appeal therefore failed.

Complaint received **20 November 1997**

Case completed **9 April 1998**

CASE AUTH/650/11/97

BOEHRINGER INGELHEIM v MONMOUTH

Letter in journal and memorandum to representatives

Boehringer Ingelheim alleged that a letter from Monmouth which had appeared in Update was untrue, misled readers about the company and disparaged Boehringer Ingelheim's product Mobic (meloxicam). The same applied to Monmouth representatives who were repeating the allegations to health professionals. The letter referred to meloxicam and stated that "Following an ABPI code of practice case, the manufacturer of this medicine has withdrawn this claim to COX-2 selectivity". Boehringer Ingelheim said that it had most certainly not withdrawn such a claim. It had merely complied with the requirement to ensure that its promotion did not mislead as to the clinical effects, if any, of this pharmacological property.

The Panel considered that the statement in the letter that "Following an ABPI code of practice case, the manufacturer of the medicine has withdrawn this claim to COX-2 selectivity" was an incorrect interpretation of the ruling in question which merely precluded Boehringer Ingelheim from claiming proven clinical benefit for COX-2 selectivity. It did not prevent the company from claiming that Mobic was COX-2 selective. The broad statement in the letter was too general and was inaccurate, misleading and disparaged Mobic. Breaches of the Code were ruled. The Panel considered that like the letter, the memorandum sent by Monmouth to its fieldforce was inaccurate, misleading and disparaged Mobic and further breaches were ruled in relation to the memorandum.

Upon appeal by Monmouth, the Appeal Board agreed with the Panel that the previous ruling precluded Boehringer Ingelheim from claiming proven clinical benefit as a consequence of COX-2 selectivity. The ruling did not prevent it claiming that Mobic was COX-2 selective. The references to Boehringer Ingelheim having withdrawn claims were too general with respect to the ruling in the previous case which referred to specific claims in a specific context. Both the letter and the memorandum were thus inaccurate, misleading and disparaged Mobic and the Appeal Board upheld the Panel's rulings that both were in breach.

Boehringer Ingelheim Limited submitted a complaint about a letter from the deputy managing director of Monmouth Pharmaceuticals Limited published in Update, 24 September 1997. Monmouth although not a member of the ABPI had nevertheless agreed to comply with the Code.

The letter, which referred to Boehringer Ingelheim's product Mobic, was a response to an article in Update 23 July 1997 entitled "Trends in the drug treatment of chronic inflammatory arthritis". The article mentioned the association between NSAIDs and gastrointestinal (GI) toxicity and stated that "Meloxicam (Mobic) and to a lesser extent nabumetone (Relifex) inhibit COX 2 to a much greater extent than COX 1; this is associated with a reduced risk of GI toxicity". The letter at issue referred to meloxicam and stated that "Following an ABPI code of practice case, the manufacturer of this medicine has withdrawn this claim to COX-2 selectivity". The letter stated that etodolac (Monmouth's product Lodine) had been shown to exhibit much of what the COX-2 selectivity theory promised, a high degree of efficacy and established gastric tolerability.

COMPLAINT

Boehringer Ingelheim alleged that the letter in Update was untrue, misled readers about the company and disparaged Mobic. Boehringer Ingelheim stated that the same complaint applied to representatives of Monmouth who repeated the allegations to healthcare professionals.

Letter in Update 24 September 1997

Boehringer Ingelheim stated that the author of the letter had cited Case AUTH/455/8/96 as the source of information in asserting that it had withdrawn its claim for Mobic of preferential or relatively selective COX-2 inhibition compared with inhibition of COX-1. Boehringer Ingelheim stated that the Panel and the Appeal Board were already aware that the property of preferential or selective COX-2 inhibition was not *per se* at issue. Boehringer Ingelheim had most certainly not withdrawn any claim to preferential or relatively selective COX-2 inhibition. It had merely complied with the requirement to ensure that its promotion did not mislead as to the clinical effects, if any, of this pharmacological property. In confirmation, Boehringer Ingelheim provided the Panel with copies of a statement made in its advertisement considered recently by the Panel and the Appeal Board and a statement regarding the pharmacological properties of meloxicam.

Boehringer Ingelheim alleged that the letter cited the Code of Practice case report incorrectly and in doing so both misled the reader and disparaged its product, thus breaching Clauses 7.2 and 8.1 of the Code.

Boehringer Ingelheim pointed out that it had also received a letter from the editor of The Practitioner which indicated that Monmouth activities with respect to meloxicam were not confined to Update . A copy of that letter was provided.

Behaviour of representatives of Monmouth

Boehringer Ingelheim stated that it had evidence that representatives of Monmouth were repeating the same allegation as part of their promotion of Lodine. Boehringer Ingelheim provided a letter from a consultant rheumatologist and an e-mail from its senior information pharmacist which referred to an enquiry from a hospital pharmacist. Boehringer Ingelheim stated that these referred to statements made by Monmouth representatives which were identical to the allegations made by Monmouth mentioned above. In each case replies had to be written to the informants - copies of which were provided. Boehringer Ingelheim alleged that in claiming, incorrectly, that it had withdrawn its claim as to the pharmacological properties of meloxicam,

Monmouth representatives were also in breach of Clauses 7.2 and 8.1

RESPONSE

Monmouth stated that in 1996 Boehringer Ingelheim launched the NSAID Mobic, claiming it was the first preferential COX-2 inhibitor and implied that this conferred upon it an improved gastrointestinal side effect profile over other NSAIDs.

In Case AUTH/455/8/96, the Panel ruled that the material was misleading and exaggerated and that the claims implied a special merit for Mobic which had not been substantiated. Upon appeal by Boehringer Ingelheim, the Appeal Board upheld the Panel's ruling.

Monmouth stated that since that time it had seen no promotional material for Mobic that repeated the COX-2 selectivity claims made in that initial promotional campaign. In fact, it had seen no express statement on meloxicam's COX-2 selectivity in Boehringer Ingelheim's promotional material since the Code of Practice case. The internal memorandum from the senior information pharmacist at Boehringer Ingelheim to its medical director, submitted by Boehringer Ingelheim with its complaint, suggested that it did not have any such material at all.

Monmouth stated that it had seen the original claims that were ruled in breach of the Code perpetuated in a number of articles that had appeared in the medical press since that ruling. Copies of the articles, namely Prescriber 5 December 1996, Update 23 July 1997 and The Practitioner August 1997 were provided.

Monmouth stated that having read these articles, it had telephoned the editors - in two instances - in order to discuss with them ways in which these articles could be corrected. The editors suggested that the company should write to them outlining its concerns, it duly did so. Update published its letter.

Monmouth submitted that it had been scrupulous in avoiding passing its own judgement on meloxicam itself and had merely sought to have the articles brought into line with the Panel's ruling and the current claims that Boehringer Ingelheim were making in respect of its product.

Monmouth stated that in the same way it had instructed its representatives that, when they were asked about Mobic's COX-2 selectivity, they were not to pass judgement on meloxicam but to ask the doctor or pharmacist to contact Boehringer Ingelheim themselves for further information.

Monmouth stated that it had no evidence that Boehringer Ingelheim had stimulated the production or encouraged the publication of these articles but that Boehringer Ingelheim had tried very hard to prevent them being corrected. Monmouth submitted that a more responsible approach would have been for Boehringer Ingelheim to have sought to have these articles corrected.

Monmouth stated that Boehringer Ingelheim cited one apparently neutrally worded and perfectly natural enquiry from a hospital pharmacist as evidence that one of these corrections was misleading.

Monmouth noted that Boehringer Ingelheim accused its representatives of "repeating the allegation" made in Monmouth's letter to Update. The evidence for this was one letter from a consultant rheumatologist who met with one of Monmouth's representatives three weeks before its letter appeared in Update. This doctor was doing exactly what Monmouth would recommend that he should do in the circumstances: contact Boehringer Ingelheim for information.

Monmouth stated that many doctors and pharmacists were confused about Boehringer Ingelheim's COX-2 selectivity claims for Mobic. When Monmouth representatives briefed these people on Lodine's COX-2 selectivity they were often asked about Mobic's. In June, Monmouth discussed this matter over the telephone with the medical director of Boehringer Ingelheim who asked Monmouth to advise any doctors or pharmacists who were unclear about its claims to contact Boehringer Ingelheim. Monmouth had passed this instruction on to its representatives.

Monmouth stated that it had on two occasions sought to have corrections made to articles that had made claims for meloxicam that Boehringer Ingelheim had made in their initial promotion of Mobic and which the company had not made since the Code of Practice case referred to earlier. Monmouth alleged that Boehringer Ingelheim had taken the statements it had made in these corrections, exaggerated them, put them into a different context, and then sought to damage Monmouth by asserting that they were being misleading and disparaging. Monmouth stated that Boehringer Ingelheim had done this not just in their letter of complaint to the Authority but also in letters to the consultant rheumatologist, the hospital pharmacist, and the editor of The Practitioner. The letter to the consultant rheumatologist was particularly unpleasant, accusing Monmouth of wilfully misleading him - without any evidence that Monmouth had seen and without any attempt to obtain a balanced view by seeking to learn from Monmouth what its representative had said.

Monmouth stated that Boehringer Ingelheim had asserted that the Deputy Managing Director of Monmouth had written prevaricating and irrelevant replies to its request that its statements be withdrawn. Monmouth stated that this was not the case. It had replied directly to its request and had asked Boehringer Ingelheim for examples of its promotional materials and details of the complaints about Monmouth's representatives, none of which it had received until receipt of this complaint.

1 Update Article 23 July and letter of 24 September 1997

Monmouth confirmed that the article on which it was commenting stated:

"Meloxicam (Mobic) and to a lesser extent nabumetone (Relifex) inhibit COX-2 to a much greater extent than COX-1; this is associated with a reduced risk of GI toxicity".

Monmouth stated that this was a claim that Boehringer Ingelheim made in its initial promotion of Mobic and which it withdrew as a direct result of the Panel ruling in Case AUTH/455/8/96. This was the claim Monmouth was asserting that Boehringer Ingelheim had withdrawn.

Monmouth stated that Boehringer Ingelheim had complained about its statement "Following an ABPI code of practice case, the manufacturer of this medicine has withdrawn this claim to COX-2 selectivity". Monmouth maintained that, in the context of its letter and the article on which it was commenting, this statement was true, did not mislead the reader and did not disparage Boehringer Ingelheim's product. Monmouth submitted that its letter made clear reference to both the article and the Code of Practice case involved. Monmouth pointed out that it had stated in the letter that the manufacturer of this medicine had withdrawn this claim to COX-2 selectivity.

Monmouth did not state that Boehringer Ingelheim had withdrawn all claims relating to COX-2 selectivity, despite the fact that they had not made a single express statement on meloxicam's COX-2 selectivity in their promotional material, since the Code of Practice case referred to earlier.

Monmouth pointed out that in its letter of complaint, Boehringer Ingelheim stated that it was asserting that it had withdrawn a claim for meloxicam of preferential or relatively selective COX-2 inhibition compared with inhibition of COX-1. This was not so. This was not the claim that was made in the article and it had not used these terms in its letter. Boehringer Ingelheim was trying to suggest that Monmouth was making a broader statement that it really was.

2 Boehringer Ingelheim's claims for meloxicam

Monmouth stated that since the Code of Practice case concerning Boehringer Ingelheim's initial claims for meloxicam, there had been much confusion over what it was now claiming for this product. It had not published the effect of the Panel's ruling and had not replaced its original claims with clear statements about meloxicam's COX-2 selectivity. It was as though Boehringer Ingelheim was hoping that the original impression created with the initial promotional campaign would be left in the minds of doctors and pharmacists without any alteration to bring it in line with the Panel ruling.

Monmouth submitted that from the correspondence with Boehringer Ingelheim's solicitors, one could see that Boehringer Ingelheim effectively accepted it was not making the claim stated in the Update article. Monmouth stated that Boehringer Ingelheim's solicitors had told Monmouth that it was making "a" claim to COX-2 selectivity, although when they went on to describe this they did so without using the words "selective" or "selectivity" at all.

Monmouth submitted that its letter made clear reference to the article on which it was commenting and made no reference to any claim that Boehringer Ingelheim was making. It was not claiming that "meloxicam inhibits COX-2 to a much greater extent than COX-1"; neither was it making an unqualified claim to COX-2 selectivity.

Monmouth stated that its evidence for this was:

a) Nowhere in Boehringer Ingelheim's promotional material, nor in its complaint, nor in any of the attachments that accompanied that complaint, did Boehringer Ingelheim claim that "meloxicam inhibits COX-2 to a much greater extent than COX-1". Monmouth stated that were Boehringer Ingelheim to make such a claim, it would certainly challenge such a claim because it believed it to be unsubstantiated.

b) Monmouth noted that in support of the complaint, Boehringer Ingelheim had submitted a journal advertisement for Mobic. This advertisement was typical of the Mobic promotional material that Boehringer Ingelheim had produced since the Code of Practice case referred to. It made some statements about the theory of COX-2 selectivity but it did not make a single express statement about meloxicam's own COX-2 selectivity. In fact it made no mention whatsoever of meloxicam's pharmacological profile.

c) The absence of an express statement on meloxicam's COX-2 selectivity in this advertisement was consistent with statements made to Monmouth by the medical director of Boehringer Ingelheim who stated over the telephone that Boehringer Ingelheim was not claiming that Mobic was COX-2 selective. In fact he went further than this and declared that no pharmaceutical company could claim COX-2 selectivity for a product. Referring to the same Code of Practice case that Monmouth had cited, he said that any product that had some COX-1 activity could not be said to be COX-2 selective. This was the view of Boehringer Ingelheim's medical director, not of Monmouth.

d) Later, on 23 June, Boehringer Ingelheim's medical director wrote Monmouth a letter of complaint in which he confirmed his view that COX-2 selectivity (unqualified) could not be claimed for a product unless it inhibited only COX-2. Monmouth submitted that given this view from its medical director, it was perhaps not surprising that Boehringer Ingelheim had not produced any promotional material that included such a claim. (It had been well established that meloxicam had some COX-1 activity and this point was accepted in the Code of Practice case, referred to previously).

e) Since the Code of Practice case referred to previously, none of Boehringer Ingelheim's promotional material had made any express statement about meloxicam's COX-2 selectivity.

f) It appeared that Boehringer Ingelheim's marketing department did not have a clear statement on meloxicam's COX-2 selectivity that they could send out in response to an enquiry from a consultant rheumatologist. The medical director, himself, had to write to him.

g) Boehringer Ingelheim's senior information pharmacist did not even know if it had a statement on meloxicam's COX-2 selectivity that she could give in response to an enquiry from a hospital pharmacist. She had to ask her medical director to handle the enquiry.

h) Monmouth stated that it had evidence from a GP (one of its medical advisors) that Boehringer Ingelheim representatives did not have any written information that they could supply on Mobic relating to COX-2 selectivity. In response to a request for such information, Boehringer Ingelheim was unable to supply it promptly.

i) There was no statement on COX-2 selectivity in Mobic's summary of product characteristics (SPC) or in the prescribing information given in its advertising.

3 Citing of Code of Practice Case AUTH/455/8/96

Monmouth pointed out that in its letter of complaint,

Boehringer Ingelheim stated that Monmouth's letter of 24 September 1997 cited the Code of Practice case report incorrectly.

The case cited concerned Boehringer Ingelheim's claims for meloxicam, one of which was that it inhibited COX-2 to a greater extent than COX-1 and that this was associated with an improved gastrointestinal side-effect profile. The COX-2 selectivity claim made in the Update article delivered the same message: "Meloxicam (Mobic) ... inhibit[s] COX-2 to a much greater extent than COX-1; this is associated with a reduced risk of GI toxicity".

According to the case report: "The Appeal Board considered that doctors would be left with the message that Mobic was a significant improvement in treatment by inhibiting COX-2 preferentially and that this resulted in an improved safety profile compared to other NSAIDs". This was exactly the point made in the Update article. The Appeal Board agreed with the Panel that overall the material was misleading and that the claims were exaggerated and implied a special merit for Mobic which could not be substantiated.

Monmouth understood that Boehringer Ingelheim had withdrawn these claims and were Boehringer Ingelheim to make such claims the company would be in breach of the Code.

Monmouth stated that it had, therefore, cited the Code of Practice case report correctly and so had not misled the reader or disparaged Boehringer Ingelheim's product.

Monmouth submitted that Boehringer Ingelheim must have been aware that the article expressed an opinion which it was disallowed from expressing itself. It had the opportunity to correct the impression given but chose not to do so. Instead, when Monmouth sought to correct this impression, Boehringer Ingelheim attacked Monmouth. Monmouth stated that it was important to make the point that it was defending the position taken by the Panel in Case AUTH/455/8/96, against attack from Boehringer Ingelheim.

Monmouth stated that a retraction of its letter, as Boehringer Ingelheim requested, would leave the impression that it was still making the claim that was in the article: that Mobic inhibited COX-2 to a much greater extent than COX-1 and that this was associated with a reduced risk of GI toxicity. This could encourage prescribing doctors to rely on a safety statement that had not been proven and might, therefore, endanger patient safety.

4 Right of reply

Monmouth stated that in order to ensure fairness and balance, it had sought and received assurances from the editor of Update that if Boehringer Ingelheim submitted a letter in response, then he would publish it and had even suggested this course of action to Boehringer Ingelheim in a letter to its solicitors (copies of this correspondence were provided to the Panel) but Boehringer Ingelheim had not taken it up. This option still remained open.

5 The Practitioner article of August 1997

Monmouth pointed out that in its letter of complaint to the Authority, Boehringer Ingelheim also referred to a letter that it had received from the editor of The Practitioner. Although Boehringer Ingelheim had not made a specific complaint relating to this, Monmouth stated that it would like to deal with this matter as well.

Like Update, The Practitioner had published an article that made a claim that Boehringer Ingelheim made in its initial promotion of Mobic but which it now no longer made.

The Practitioner article stated that "Selective inhibitors of COX-2 have recently been developed, with meloxicam being the first to be licensed". Monmouth stated that this was not true. Lodine (etodolac) was licensed in the UK eleven years before Mobic. High quality work demonstrating etodolac's COX-2 selectivity was published in an international, peer-reviewed journal of good repute a year before Boehringer Ingelheim introduced Mobic. Monmouth had telephoned the editor to ask for a correction to be made. The editor had explained that they did not have a regular letters page but that if Monmouth would write to him he would consider the matter. So Monmouth wrote a letter to him. With the agreement of Monmouth, the editor then sent its letter to Boehringer Ingelheim for its response before he published anything.

Monmouth stated that several weeks went by without any response being received from Boehringer Ingelheim, so it asked the editor to make further enquiries. As far as it could tell, the first response that Boehringer Ingelheim had made to this was its letter to The Practitioner of 19 November. The first that Monmouth was aware that it had responded at all was when it received a copy of this letter which the Authority had sent to Monmouth with Boehringer Ingelheim's complaint.

Since then the editor had also written to Monmouth and discussed the matter further over the telephone. The editor did not want to publish an erratum until he knew the outcome of this case.

Monmouth pointed out that in its view the erratum proposed by the editor did not address the error: the claim that meloxicam was the first selective inhibitor of COX-2 to be licensed in the UK. Monmouth had written to The Practitioner to point this out and to repeat its request that an appropriate correction be published.

Monmouth noted that Boehringer Ingelheim's letter to The Practitioner cited Professor Sir John Vane as agreeing that there was nothing basically wrong with the statement made in this article. Monmouth had written to ask Professor Sir John Vane to confirm this and he had replied that in his view the article should be changed.

6 Etodolac's COX-2 selectivity on Lodine/Lodine SR data sheet

Monmouth stated that because of the controversy surrounding Boehringer Ingelheim's Mobic COX-2 selectivity claims, it had the work on etodolac's COX-2 selectivity submitted to the Medicines Control Agency (MCA) earlier this year with a request that the product licence be varied to include a statement on etodolac's COX-2 selectivity. This variation was granted and it had subsequently changed the data sheet to reflect this.

This was in marked contrast to Boehringer Ingelheim's

summary of product characteristics for Mobic which carried no statement regarding the COX-2 selectivity of meloxicam.

7 Behaviour of Monmouth representatives

Monmouth stated that Boehringer Ingelheim complained that Monmouth's representatives were "repeating the same allegation" as part of their promotion of Lodine. If by this they meant that Monmouth representatives were making disparaging remarks about Mobic then Boehringer Ingelheim was incorrect.

Monmouth stated that it should be noted that the only evidence Boehringer Ingelheim had submitted consisted of two items to support this complaint. Monmouth submitted that the two items did no such thing. In fact they simply illustrated the difficulty that doctors and pharmacists had in obtaining any clear statement from Boehringer Ingelheim concerning Mobic and COX-2 selectivity.

There seemed to be a lot of confusion amongst doctors and pharmacists over the COX-2 selectivity claims of Boehringer Ingelheim. Monmouth stated that its representatives were often asked about the COX-2 selectivity of Mobic.

8 Briefing of Monmouth representatives

Monmouth stated that it had repeatedly and consistently briefed its representatives at regional and national meetings on how to handle these enquiries. Recently it had written to remind all of its representatives of the procedure it wished them to follow in these circumstances. Monmouth provided a copy of this briefing document.

Monmouth stated that one could see from this document that it had instructed its representatives to refrain from commenting on meloxicam's COX-2 selectivity themselves. Instead, the representatives were instructed to refer the doctor to Boehringer Ingelheim.

9 Letter from a consultant rheumatologist

Monmouth referred to the letter from a consultant rheumatologist provided by Boehringer Ingelheim.

In the letter the consultant had stated that he could not remember exactly what its representative said to him. The consultant seemed confused over several aspects of the matter.

Monmouth confirmed that one of its representatives did see the consultant on 3 September, six weeks before his letter of 13 October to Boehringer Ingelheim. This was shown in the weekly hospital call report from that time. It was confirmed by the contemporaneous notes made by this representative in his hospital records and in the signed statement that was prepared as a result of the enquiry Monmouth had held on receiving details of the complaint.

10 Statement from Monmouth's representative

Monmouth submitted that the account of the meeting given in the representative's statement showed clearly that this representative behaved quite correctly and followed the procedure on which he had been briefed.

Monmouth emphasised that he had been employed as a representative with Monmouth for over a year. In that time he had never given cause to doubt his honesty. He came from a good background, was a science graduate and had passed his ABPI representatives examination.

Monmouth stated that the following points should be noted about the representative's statement:

a) It was entirely consistent with his weekly hospital call report and his contemporaneous notes made in his hospital records.

b) Because it was one of his first meetings with a consultant rheumatologist the representative remembered it very well. This was illustrated by the details that he was able to recall when making his recent statement, such as the delay to the start and the total length of the meeting.

c) The representative briefed the consultant on four of the company's products in 15 minutes. This would not have left much time for a detailed discussion about a competitor.

d) It was the consultant who raised the subject of meloxicam and asked about its COX-2 selectivity.

e) The representative did not make any assertions of his own about meloxicam, he merely referred to the Code of Practice case, Boehringer Ingelheim's own promotional material and suggested that the consultant contact Boehringer Ingelheim for further information about meloxicam's COX-2 selectivity (which he did).

f) The nature and length of the discussion about meloxicam were such that it did not even merit a mention in the representative's records which were primarily written to be of assistance in the planning of future meetings with the doctor. Clearly these records provided evidence that the representative had no intention of capitalising on the confusion in the consultant's mind over meloxicam's COX-2 selectivity at future meetings.

g) The representative did explain that the product licence for Lodine had been varied and the data sheet changed to include information about etodolac's COX-2 selectivity. He also stated that as far as he knew Lodine was the only product to have such information on its data sheet.

h) In the light of the statement from the representative, Monmouth saw that it was entirely possible that later - six weeks later - the consultant found himself wondering:

i) That as Lodine had COX-2 selectivity on its data sheet and Mobic did not, perhaps the Mobic product licence was going to have to be changed.

ii) Whether Boehringer Ingelheim could continue to make a claim to "the specific COX-2 activity of Mobic" without such a change to its product licence.

Monmouth stated that the evidence showed that its representative followed the procedure on which he had been briefed.

The important thing was that the consultant sought clarification about COX-2 selectivity in relation to meloxicam from Boehringer Ingelheim. This was the outcome that its representatives were instructed to aim for. Monmouth was pleased to see that in this case it was

successfully achieved.

11 Enquiry from a hospital pharmacist

Monmouth pointed out that the other item that Boehringer Ingelheim had submitted was an internal communication from one of its employees to another. This was a request from a senior information pharmacist at Boehringer Ingelheim who was asking her own medical director to supply a written statement about COX-2 selectivity in relation to meloxicam and asked "Do we have one?".

It was perfectly natural that, on reading that Boehringer Ingelheim had withdrawn one of its original claims, this hospital pharmacist wanted to know what it was that they were currently claiming on COX-2 selectivity. Since this was not apparent from its promotional material, he really had little option but to contact the company and ask for a clear statement on this matter.

Although Boehringer Ingelheim submitted this item as evidence that Monmouth's representatives were disparaging about their product, it did not refer to Monmouth's representatives at all. Monmouth confirmed that none of its representatives had met with the hospital pharmacist to discuss either Lodine or meloxicam.

12 Conclusion

Monmouth submitted that it was quite proper for it to seek to have corrections made to articles in the medical press that were misleading and it had done this in a responsible way that did not breach the Code.

Its representatives had been properly briefed on how to handle enquiries about meloxicam's COX-2 selectivity and they were following the correct procedure when this arose.

There was a lot of confusion over Boehringer Ingelheim's claims for meloxicam in relation to COX-2 selectivity but this was not of Monmouth's making. Monmouth submitted that it was doing all that it could in these circumstances to refer such enquiries to Boehringer Ingelheim so that Boehringer Ingelheim could address the matter.

PANEL RULING

The Panel noted Case AUTH/455/8/96 which concerned the promotion of Mobic. In that case the Panel accepted that it had been established that NSAIDs had different COX-2:COX-1 inhibition ratios and that there was some evidence that the difference in the levels of gastrointestinal side effects correlated with this ratio. There was insufficient evidence on the use of highly selective COX-2 inhibitors to establish that this theoretical concept translated into definite clinical benefit. Boehringer Ingelheim was ruled in breach of Clauses 7.2 and 7.8 of the Code. The Panel's ruling was upheld by the Appeal Board.

Turning to the case now before it, the Panel noted that the letter in Update stated that the original article in Update had stated that "... meloxicam inhibits COX-2 to a much greater extent than COX-1". The letter went on to state that "Following an ABPI code of practice case, the manufacturer of this medicine has withdrawn this claim to COX-2 selectivity". The Panel considered that this was an incorrect interpretation of the ruling in Case AUTH/455/8/96 which merely precluded Boehringer Ingelheim from claiming proven clinical benefit for COX-2 selectivity. The ruling did not prevent Boehringer Ingelheim claiming that Mobic was COX-2 selective.

The Panel considered that the statement in the letter was too general with respect to the previous Code of Practice case. The previous ruling had related to specific claims made in a specific context. The broad statement in the letter was thus inaccurate, misleading and disparaged Mobic. The Panel therefore ruled breaches of Clauses 7.2 and 8.1 of the Code.

The Panel noted that a memorandum addressed to Monmouth's UK field force, entitled "Boehringer Ingelheim and COX-2 claims" stated that "Boehringer Ingelheim lost an ABPI Code of Practice case on their original COX-2 claims. We understand that they have withdrawn those original claims. Since then we have not seen any written promotional material from Boehringer Ingelheim that claims meloxicam is COX-2 selective". The Panel considered that, like the letter, this memorandum was too general. In the Panel's view the memorandum wrongly suggested that the ruling in Case AUTH/455/8/96 precluded Boehringer Ingelheim from claiming that Mobic was COX-2 selective. The actual ruling had been much more specific than that.

The Panel noted that the Monmouth representative had told the consultant rheumatologist that "... following a Code of Practice case Boehringer had withdrawn their initial advertising for meloxicam in which some claims relating to COX-2 selectivity had been made and that since then we had not seen any COX-2 selectivity claims for meloxicam in their advertising". In the Panel's view the representative had adhered to the memorandum sent to the field force. The Panel considered that, like the letter, the message conveyed by the field force was inaccurate, misleading and disparaged Mobic. Breaches of Clauses 7.2 and 8.1 were ruled.

APPEAL BY MONMOUTH

1 Letter in Update

Monmouth stated that the Panel had ruled that it was in breach of Clauses 7.2 and 8.1 of the Code because the statement in its letter to Update was too general with respect to the previous Code of Practice case. The Panel commented that the ruling in Case AUTH/455/8/96 did not prevent Boehringer Ingelheim from claiming that Mobic was COX-2 selective.

Monmouth did not say in its letter to Update that this case prevented Boehringer Ingelheim from claiming that meloxicam was COX-2 selective (even though Boehringer Ingelheim led Monmouth to believe that this was its interpretation of that ruling). Neither did Monmouth say that Boehringer Ingelheim had withdrawn the claim that meloxicam was COX-2 selective *per se* (even though Boehringer Ingelheim told Monmouth that it had).

It seemed that the Panel concluded that Monmouth was implying that Boehringer Ingelheim was not claiming that meloxicam was COX-2 selective *per se*.

Monmouth did not and neither did it intend to imply this in that letter. Monmouth stated that its original response described how that letter referred specifically to the particular claim made in the article. It had also to be remembered that:

i) The letter was only published in the journal in which the article making the specific prohibited claim appeared.

ii) The article was clearly referred to in the letter.

iii) The editor had assured Monmouth that should Boehringer Ingelheim wish to submit a reply to modify or respond to Monmouth's letter, that he would publish it. Monmouth even suggested this course of action to Boehringer Ingelheim's solicitors but they appeared not to have taken it up.

There was a very important aspect of this matter that Monmouth believed the Panel had overlooked: at the time that Monmouth wrote the letter it had been led to believe by Boehringer Ingelheim itself that it was not claiming that meloxicam was COX-2 selective.

Details on this were submitted in Monmouth's original response but the Appeal Board's attention was particularly drawn to the following points:

a) Boehringer Ingelheim's medical director told Monmouth that it was not claiming that meloxicam was COX-2 selective.

b) Boehringer Ingelheim's medical director wrote to Monmouth stating very clearly the criteria which it believed had to be met in order for a claim of COX-2 selectivity to be made. Meloxicam did not fulfil these criteria.

These statements from the medical director of Boehringer Ingelheim were consistent with its promotional material which made no express statement about meloxicam's selectivity.

Under these circumstances, Monmouth would not have been in breach of the Code even if it had expressly stated that Boehringer Ingelheim was not claiming that meloxicam was COX-2 selective *per se*, let alone if Monmouth had inadvertently implied such a thing. Monmouth would only have been repeating the view of Boehringer Ingelheim's medical director which surely could not be inaccurate, misleading and disparaging of Mobic.

As the letter of 23 June 1997 from Boehringer Ingelheim's medical director was such an important piece of evidence in this case, Monmouth asked the Appeal Board to study it closely.

Monmouth's medical advisor had written back to Boehringer Ingelheim's medical director in reply clarifying that "The main difference between our advertising and yours is that we are claiming that Lodine is COX-2 selective and are giving information about this, whilst you are not making such a claim or giving such information about Mobic.". Boehringer Ingelheim did not deny that this was the situation. In fact, Monmouth stated that it had received no further correspondence or telephone calls from Boehringer Ingelheim on this subject until its solicitors wrote to Monmouth on 17 October after Case AUTH/583/7/97 was completed and had concluded that Boehringer Ingelheim could claim that meloxicam was COX-2 selective after all and that this was permitted.

Boehringer Ingelheim only seemed to have changed its view on whether the ruling in Case AUTH/455/8/96 prevented it from making this claim when the Panel initially ruled that it was in breach of the Code in Case AUTH/583/7/97. Then, at the appeal stage, Boehringer Ingelheim found it expedient to accept the finding that its advertising did imply this claim after all and switched its defence to saying that it was not in breach of the Code because it had dissociated the COX-2 selectivity claim from the claim of clinical benefit.

It was at this point, having realised that it was not prevented from making this claim to COX-2 selectivity *per se*, and having been found to have been making it in any case, that Boehringer Ingelheim challenged Monmouth for implying that Boehringer Ingelheim was not making this claim. Boehringer Ingelheim seemed to have ignored the fact that it had told Monmouth that no one could make this claim and that it had written to Monmouth outlining the criteria which it believed had to be met before such a claim could be made.

Monmouth provided a summary of the timing of the key communications as it considered that the chronology of the events was of critical importance.

2 Memorandum to representatives

Monmouth noted that the Panel concluded that the Monmouth representative had adhered to the memorandum sent to the field force. It also concluded, however, that, like the letter to Update, the memorandum wrongly suggested that the ruling in Case AUTH/455/8/96 precluded Boehringer Ingelheim from claiming that Mobic was COX-2 selective.

Many of the points Monmouth made in relation to the letter in Update also applied to the memorandum to its UK field force. The following applied particularly to the memorandum itself:

i) The memorandum was a reminder of earlier briefings on how to handle doctors' questions about meloxicam's COX-2 selectivity. It was written later than the letter to Update, on 10 November 1997. By this time it was clear (from its solicitors' letters) that Boehringer Ingelheim had shifted its stance on whether or not it was claiming that meloxicam was COX-2 selective. This made the first point in the memorandum especially relevant "We are not clear exactly what Boehringer Ingelheim are claiming for meloxicam in this respect".

ii) Monmouth had never said that Case AUTH/455/8/96 precluded Boehringer Ingelheim from claiming that meloxicam was COX-2 selective. The memorandum did not suggest this at all. In fact the wording in the first point particularly allowed for the possibility that Boehringer Ingelheim might now be making such a claim - despite its earlier statements to Monmouth on this subject.

iii) The memorandum expressly reminded Monmouth's representatives that "we ourselves are not commenting on meloxicam's selectivity". This was included in order to make it clear to representatives that they must not say anything one way or another about meloxicam's COX-2 selectivity. It should be remembered that on the one hand

Boehringer Ingelheim's medical director had told Monmouth that it was not making a claim of COX-2 selectivity and that in his view no one was able to make such a claim; on the other hand its solicitors had written to Monmouth indicating that some sort of "preferential inhibition" claim was being made although no promotional material supporting this had been sent to Monmouth in response to its request for such material. It should be noted that Boehringer Ingelheim did not inform Monmouth that in Case AUTH/583/7/97 the Appeal Board had ruled that meloxicam was COX-2 selective and that it now accepted that such a claim could be made. The case report for that case had not been published at that time, so Monmouth had no knowledge of this ruling and could not have updated the briefing to its representatives in the light of this development.

iv) All the statements in the memorandum were true and it was carefully worded to leave a wide variety of options open to Boehringer Ingelheim for its meloxicam claims.

3 Conclusion

Neither in Monmouth's letter to Update nor in the memorandum to its representatives did Monmouth say that Case AUTH/455/8/96 precluded Boehringer Ingelheim from claiming that meloxicam was COX-2 selective. Neither did Monmouth say that meloxicam was not COX-2 selective *per se*. If it could be said that Monmouth inadvertently implied that Boehringer Ingelheim was no longer claiming that meloxicam was COX-2 selective *per se*, then Monmouth would only have been repeating what Boehringer Ingelheim, itself, had told Monmouth. Monmouth, therefore, believed that it was not inaccurate, misleading and disparaging of Mobic and consequently asked the Appeal Board to rule that it was not in breach of the Code.

4 Background information

Monmouth considered that the general context in which this case had arisen should not be forgotten.

Prior to the launch of meloxicam, Boehringer Ingelheim hyped up the COX-2 selectivity theory.

It then launched meloxicam claiming that it was "the first preferential COX-2 inhibitor", despite the fact that etodolac (Lodine) had been available in the UK for 11 years and had had its COX-2 selectivity reported in peer reviewed published literature a year before the meloxicam launch.

It also implied that COX-2 selectivity conferred a special clinical benefit upon meloxicam, namely a gastrointestinal side effect profile that was superior to other NSAIDs.

To launch a new NSAID and imply a GI safety claim based on an unproven pharmacological theory, was, in Monmouth's view, irresponsible. Monmouth noted that the original promotional material for Mobic had been ruled in breach of the Code.

Since that ruling Boehringer Ingelheim had withdrawn those initial claims but Monmouth had seen those same claims perpetuated in articles published in the medical press. When Monmouth pointed out in one of the journals that such a claim had been withdrawn, Boehringer Ingelheim attacked it.

Monmouth supplied a copy of a Dear Doctor warning letter dated 16 December 1997 from Boehringer Ingelheim. This showed that vulnerable patients had been treated with meloxicam and some of these had suffered GI bleeds, ulcers and perforations.

Because of the controversy in this area, both Boehringer Ingelheim and Monmouth had been submitting their promotional materials for Mobic and Lodine to the MCA for approval prior to use. There were, however, large differences in the claims that were being made for these products. The MCA had approved (or accepted that it had no objections to) very different statements relating to these two different products. Monmouth was currently producing new promotional materials for Lodine and it provided copies of the main MCA approved detail aid.

5 Actions taken since the Panel ruling

As a direct result of receiving notice of the Panel's ruling in this case, Monmouth had taken the following actions:

i) It had withheld a letter which the editor of The Pharmaceutical Times had agreed to publish commenting on another article that made a prohibited claim for meloxicam. Copies of the article and the letter that Monmouth had prepared for publication were provided.

ii) Monmouth had amended its instructions to its representatives by sending them a memorandum to replace earlier briefings on the handling of the subject of meloxicam's COX-2 selectivity. A copy was provided.

Monmouth did not want these actions to undermine its appeal in this case.

APPEAL BOARD RULING

The Appeal Board agreed with the Panel that Case AUTH/455/8/96 precluded Boehringer Ingelheim from claiming proven clinical benefit as a consequence of COX-2 selectivity. The ruling did not prevent Boehringer Ingelheim claiming that Mobic was COX-2 selective.

The Appeal Board considered that the references to Boehringer Ingelheim having withdrawn claims for COX-2 selectivity in both the letter in Update and the memorandum to representatives were too general with respect to the ruling in the previous case which referred to specific claims in a specific context. Both the letter and the memorandum were thus inaccurate, misleading and disparaged Mobic. The Appeal Board upheld the Panel's rulings that each item was in breach of Clauses 7.2 and 8.1 of the Code.

The appeal therefore failed.

Complaint received **20 November 1997**

Case completed **14 April 1998**

GENERAL PRACTITIONER and DIRECTOR/MEDIA v EISAI and PFIZER

Aricept advertisement

In Cases AUTH/651/11/97 & AUTH/652/11/97, a general practitioner complained about a journal advertisement for Aricept (donepezil) issued jointly by Eisai and Pfizer. The advertisement was headed "Mum has Alzheimer's" beneath which was a photograph of an elderly woman and her daughter both smiling. A smaller photograph showed the daughter looking worried. Beneath the larger photograph was the phrase, running on from the heading, "but she knew I was calling today". The complainant said that the main claim, because of the large and bold font used, was that the carer would notice an improvement in her mother's Alzheimer's disease because of treatment with the medicine. The advertisement referred to three articles, all of which stated that quality of life parameters as assessed by both carers and patients were no different to placebo. The complainant alleged that the claim was unsubstantiated.

Cases AUTH/659/12/97 & AUTH/660/12/97 arose from a letter in the British Medical Journal which was critical of the same advertisement and which was taken up as a complaint in accordance with established procedure. The author of the letter alleged that the caption "Mum has Alzheimer's but she knew I was calling today" was a powerful claim for efficacy in a condition currently believed to be incurable and relentlessly progressive. Commenting on a published trial referenced in the advertisement, the author said that it was highly likely that the differences attributed to the intervention could have arisen by chance. Other studies had shown smaller differences between intervention and control groups.

The allegations made in these cases were similar to those made in two complaints already dealt with by the Authority in which the Panel had ruled no breach of the Code (Cases AUTH/561/5/97 & AUTH/562/5/97 and Cases AUTH/593/8/97 & AUTH/594/8/97). The rulings in those cases had not been appealed and the Authority's Constitution and Procedure allowed that the new cases could proceed notwithstanding the fact that they covered similar ground to those previously decided.

Having reviewed its rulings in those previous cases, the Panel decided that its rulings in them applied also to the new cases and accordingly ruled that there had been no breach of the Code.

Upon appeal by both complainants, the Appeal Board's view was that the combination of the photograph of the mother and daughter and the wording "but she knew I was calling today" gave the impression that the patient's memory improved following treatment with Aricept. The Appeal Board noted that the data supplied by the companies showed that the decline in cognitive function in patients with Alzheimer's was slowed following treatment with Aricept compared to treatment with placebo. Memory was only one of the elements of cognitive function. It had not been studied separately. A change in cognitive function could be due to elements other than memory. The Appeal Board accepted that there were some patients who might experience an improvement in cognitive function. There was, however, insufficient data to support the impression given by the advertisement that memory in particular improved following treatment with Aricept. The advertising was not a balanced view of the data. The Appeal Board therefore ruled that there had been a breach of the Code, the appeals thus being successful.

CASES AUTH/651/11/97 & AUTH/652/11/97

A general practitioner submitted a complaint about an Aricept advertisement (A039-30130-06-97) which had appeared in a number of medical publications. The advertisement was headed "Mum has Alzheimer's" beneath which was a large coloured photograph of an elderly woman and her daughter, both smiling. Partially super-imposed on the top right hand corner of this photograph was another, much smaller, photograph of the daughter looking worried. Beneath the large photograph was the phrase, which ran on from the heading, "but she knew I was calling today". The advertisement was jointly issued by Eisai Limited and Pfizer Limited.

COMPLAINT

The complainant alleged that the advertisement was in breach of Clause 7.2 of the Code. The main claim, because of the bold and large font used, was that the carer would notice an improvement in her mother's Alzheimer's disease because of treatment with the medicine. The advertisement referred to three articles, all of which stated that quality of life parameters as assessed by both carers and patients were no different from placebo. The complainant therefore concluded that the claim was unsubstantiated.

* * * * *

The Authority noted that this advertisement was similar to the advertisement at issue in Cases AUTH/561/5/97 & AUTH/562/5/97 in which the Panel had ruled no breach of the Code. Paragraph 5.1 of the Constitution and Procedure for the Prescription Medicines Code of Practice Authority stated that 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 appeal to the Code of Practice Appeal Board.

Eisai and Pfizer agreed with the Authority that this complaint was similar to the previous complaint and that the responses in Cases AUTH/561/5/97 & AUTH/562/5/97 would apply to the new cases.

Previously decided Cases AUTH/561/5/97 & AUTH/562/5/97

The allegations in Cases AUTH/561/5/97 & AUTH/562/5/97 concerned the fact that there had been one published randomised controlled trial of the use of donepezil in Alzheimer's disease and this had shown no improvement in the quality of life of carers and that the

advertisement suggested an unrealistic improvement in the mental status of patients.

RESPONSE

Eisai had submitted on behalf of both companies that the principal claim made by the advertisement was the improvement in cognitive function of the patient, rather than in the quality of life of the care-giver. This claim was supported by the summary of product characteristics (SPC) and two pivotal phase III studies.

The SPC stated that: "In two double-blind randomised trials, statistically significant drug placebo differences were present for each of the two primary outcome measures (ADAS-cog/CIBIC plus)". The ADAS-cog scale was one of the most widely used measures of cognition in major therapeutic trials of Alzheimer's disease.

Study 301 showed a statistically significant improvement in ADAS-cog measures over the 12 week treatment period. It showed loss of treatment effect during the placebo washout phase. Study 302, which had been accepted for publication in Neurology, showed a statistically significant improvement in ADAS-cog over the 24 week study period and again the washout period provided evidence of treatment effect.

In the phase III studies, the quality of life of the care-giver was not an efficacy end-point. As secondary efficacy variables, patient quality of life was assessed although the studies were not designed to show statistical differences between treatment groups. In both studies, 301 and 302, patient quality of life measurements did not show statistically significant differences between the groups.

Eisai submitted that the photograph and wording were not intended to, and did not, claim or imply an improved quality of life of the care-giver. An issue incidental to the message conveyed by the advertisement which concentrated on the patient's condition. The photograph showed that a daughter (who was not even necessarily the primary care-giver) was pleased that her mother's condition had been improved by her new medication. Eisai submitted that this was a natural and self-evident reaction and did not require specific substantiation. It was fair to reflect the daughter's happy mood in the photograph this way.

Eisai submitted that the advertisement was fair and not misleading in any way, and that the claim actually made (as opposed to that which had been inferred) was capable of substantiation and was therefore in conformity with Clauses 7.2 and 7.3 of the Code.

PANEL RULING

The Panel noted its ruling in the previous cases, Cases AUTH/561/5/97 & AUTH/562/5/97.

Previous Ruling in Cases AUTH/561/5/97 & AUTH/562/5/97

The Panel had noted that Aricept was licensed for the symptomatic treatment of mild or moderate dementia in Alzheimer's disease. It was perfectly reasonable for it to be promoted to healthcare professionals. The Panel did not accept the allegation that the advertisement suggested an unrealistic improvement in the mental state of the patient. No breach of Clauses 7.2 and 7.3 was ruled.

The Panel had noted that the two photographs in the advertisement portrayed, in the small photograph, a daughter looking worried about her mother's condition and, in the large photograph, the daughter and mother both looking pleased.

The copy above the photograph stated "Mum has Alzheimer's" with the statement "but she knew I was calling today" appearing beneath the large photograph. The Panel considered that the daughter might not be the primary carer. The Panel did not accept that the photographs implied that Aricept would have a positive effect on a carer's mood. The photographs simply portrayed a natural reaction between mother and daughter. The Panel considered that the photographs were reasonable and were not misleading in terms of any implied claim for Aricept. No breach of Clause 7.2 of the Code was ruled.

Panel Ruling in the new Cases AUTH/651/11/97 & AUTH/652/11/97

The Panel considered that its ruling in Cases AUTH/561/5/97 & AUTH/562/5/97 regarding the daughter's mood would also apply to the new complaint. The Panel therefore ruled no breach of Clause 7.2 of the Code.

The Panel noted that the new complainant had alleged that the claim that the carer would notice an improvement in her mother's condition because of treatment with the medicine was unsubstantiated. Given the previous ruling of no breach of Clause 7.2 the Panel considered that there was no breach of Clause 7.3 of the Code and ruled accordingly.

APPEAL BY THE COMPLAINANT

"The first selective treatment for the symptoms of mild or moderate dementia in Alzheimer's disease licensed in the UK."

The complainant stated that although the medicine had been granted a licence, and taking the definition of symptom as "a term applied to any evidence of disease; the term physical sign being applied to symptoms which the patient does not complain about but which are elicited upon examination", there was no published evidence cited in the advertisement to support symptomatic relief. There was no evidence therefore that administration of Aricept would result in the mother benefiting enough to realise "but she knew I was calling today".

The photographs

The complainant stated that these clearly showed an improvement in the daughter's mood. There was some confusion as to whether the daughter was the caregiver; this could be reasonably assumed as most caregivers were daughters. Eisai had submitted that the photograph and the wording were not intended to, and did not claim or imply, an improved quality of life of the caregiver. The complainant referred to pages from a mailing (A042-30116-08-97) which he had received recently from Eisai

and Pfizer. The first page was the picture of the worried daughter, the second page was research data, the third page was the happy couple together with the words "but she knew I was calling today", "Aricept ... a first step in Alzheimer's". These photographs were the same as in the advertisement. The sequence clearly implied that the medicine would benefit the patient and that the daughter was happy because of this. It was disingenuous of Eisai to claim that the photographs had nothing to do with the claimed benefits of treatment with Aricept. Advertising was very expensive and pharmaceutical companies spent a significant proportion of their budgets on bringing attention to their products in as favourable light as possible. If the photographs were not meant to enhance a reader's view that Aricept would significantly benefit a patient and carer(s) then why was it there? Surely experienced advertisers would have realised that this association could be made, and if this was not the main aim of the advertisement then it should have been changed.

The published evidence

Dementia 1996; 7:293-303

"The QoL-C also showed marked inter-subject variability with no statistical evidence of improvement over placebo in any donepezil treatment groups, suggesting that caregivers may not be useful informants about the patient's inner feelings."

The unpublished evidence

Study A301

"For the QOL scores, the results were highly variable both within and between patients and thus considered unreliable ... The QOL Scale as assessed by patients was highly variable and thus not easily interpretable."

Study A302

"The QOL scores did not show any statistically significant differences at any post-baseline on-treatment visit ... E2020 had no impact on QOL as assessed by patients."

The complainant stated that whilst the published data precluded the daughter noticing any benefit from Aricept on her mother's illness, the unpublished studies also showed that the patient did not appreciate any benefit either.

RESPONSE FROM EISAI AND PFIZER

Responding on behalf of both companies, Eisai said that the initial letter of complaint in this case referred to an advertisement for Aricept similar to the advertisement at issue in Case AUTH/561/5/97 & AUTH/562/5/97. The complainant's letter of appeal referred to a recent mailing to doctors in terms similar to the initial advertisement.

The complainant stated that "there is no published evidence cited in the advertisement to support symptomatic relief". Eisai referred to the summary of product characteristics (SPC) which clearly stated that Aricept was indicated for the "symptomatic treatment of mild to moderately severe Alzheimer's dementia". Both the advertisement and the mailing contained brief prescribing information which was consistent with the SPC. Therefore Eisai did not accept that there had been any breach of Clauses 7.2 or 7.3 of the Code on this point.

The complainant's initial letter referred to the advertisement's implied claim that the carer/ daughter would notice an improvement in her mother's Alzheimer disease because of treatment by the medicine. The complainant claimed that this was unsubstantiated by the most up to date evidence. The complainant in the initial letter and letter of appeal dismissed the published and unpublished data solely on the grounds that Aricept did not show an improvement in the quality of life measures.

Eisai referred to the guidelines published by the Committee for Proprietary Medicinal Products (CPMP) for the treatment of Alzheimer's disease. Section 2.2.5 gave an accurate account of quality of life measures in Alzheimer's disease. It was widely accepted by clinicians experienced in the study of Alzheimer's disease that there were no accurate or validated scales available to measure quality of life. The US and European authorities were consistent in demanding assessment of cognitive function and global function and the CPMP requested a measure of Activities of Daily Living.

The Dementia publication, mentioned by the complainant, clearly stated that it was a preliminary dose ranging study. It showed a statistically significant effect on cognitive function of the Aricept 5mg dose. This dose was selected as the minimal effective dose for the pivotal studies. This study was not used in isolation to support efficacy claims.

The complainant referred to unpublished evidence (Studies 301 and 302) but ignored the prime efficacy variables and concentrated on the quality of life measures. Eisai pointed out that Study 302 was now published in the peer reviewed journal Neurology. Study 301 showed clear improvements in cognitive function against placebo at all points after the 3 week assessment and against baseline at endpoint. Study 302 showed similar responses over a six month period. Both studies showed a significant placebo response as would be expected in this type of study and both showed loss of treatment effect during the placebo washout phase.

The CIBIC plus measure showed an improvement in the mean scores of global function relative to the placebo group in both studies.

The complainant also challenged the use of photographs showing an improvement in the daughter's mood. Eisai referred to previous correspondence and to the following paragraph from the Panel's ruling in Case AUTH/561/5/97 in which Eisai's position was stated as follows:

"Eisai submitted that the photograph and wording were not intended to, and did not, claim or imply an improved quality of life of the care-giver. An issue incidental to the message conveyed by the advertisement which concentrated on the patient's condition. The photograph showed that a daughter (who was not even necessarily the primary care-giver) was pleased that her mother's condition had been improved by her new medication. Eisai submitted that this was a natural and self-evident reaction and did not require specific substantiation. It was fair to reflect the daughter's mood in the photograph this way."

The complainant in the letter of appeal stated that "the sequence (of photographs and data) clearly implies that the drug will benefit the patient and that the daughter is happy because of this.". Eisai did not dispute this interpretation which it believed was fair and balanced.

The quality of life measures in the pivotal studies were secondary efficacy variables which had not been used in any of the product claims and the picture did not imply such an improvement in these scores. The core symptoms of Alzheimer's disease were the reduction of cognition and global function, and these were therefore used as primary efficacy variables. Improved cognition included memory and orientation. The data supported the benefit of Aricept in terms of improved cognition (measured by ADAS-cog and MMSE scores) and global function (measured by CIBIC and CDR-SB). It was reasonable to portray a daughter as being happy that her mother had experienced such benefits in these relevant core symptoms.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant said that he would like to ask that the January 1998 paper be excluded as 'evidence' as this was not referenced in the advertisements concerned. However, if this was not acceptable, the complainant referred to secondary efficacy parameters which showed similar results to the previous studies.

The complainant proposed that the primary efficacy data of the studies quoted were not equatable with symptoms. ADAS-cog, CIBC plus, etc were clinical scoring systems and not necessarily representative of what patients and their carers complained to their doctors about. What improvement was needed on these scoring systems to really matter to patients and their carers, ie at what score improvement would their symptoms improve and be noticed? No target figures were given for this effect. It was not enough for the papers to demonstrate a quantitative effect, they must also demonstrate a qualitative effect for the photographs used in the advertisements to be acceptable, which they did not.

The complainant was confused by the wording and meaning of the Panel's previous ruling. From the published and unpublished evidence at the time of the advertisements, a) there was no evidence that the patient's condition would improve qualitatively and b) carers would not notice any qualitative improvements either, ie the mother's condition would not improve on donepezil to a degree sufficient enough for the daughter to notice and so would not have reason to be happy in the setting of the advertisement. Further, this view was supported by Dementia 1996:7:298, 'Secondary Efficacy Parameters' ... caregivers may not be useful informants about the patient's inner feelings.

APPEAL BOARD RULING

The Appeal Board noted that Clause 7.5 of the Code required that when promotional material referred to a published study, clear references had to be given. This was the only requirement relating to references. Claims etc had to be capable of substantiation and it was possible for companies to use unpublished data to substantiate claims in promotional material. The data had to be supplied without delay following a request from a healthcare professional as required by Clause 7.4 of the Code.

The Appeal Board noted that Aricept was the first medicine licensed for use in Alzheimer's disease. In such a new area of medicine it was important that doctors clearly understood what might be expected from treatment. The Appeal Board noted that a "Dear Doctor" letter supplied by Eisai stated that "Aricept cannot halt the progression of the disease but it may improve or arrest the decline of cognitive function...".

The SPC dated March 1997 stated that Aricept was indicated for the symptomatic treatment of mild or moderate dementia in Alzheimer's. The SPC had been updated on 1 July 1997. This gave the indication as the symptomatic treatment of mild to moderately severe Alzheimer's dementia. The SPC stated that duration of treatment had not been investigated in placebo controlled trials beyond 6 months and upon discontinuation of treatment a gradual abatement of the beneficial effects of Aricept was seen. The SPC also stated that Aricept could not be considered to have any effect on the progress of the disease. The SPC included a chart which gave details of the percentage of patients who were judged treatment responders at doses of 5mg or 10mg of Aricept. The SPC defined responders as having an improvement of ADAS-cog of at least 4 points, no deterioration of CIBIC (the clinical interview based impression of change with caregiver input, a measure of global function) and no deterioration of activities of Daily Living Subscale of the Clinical Dementia Rating Scale (a measure of capabilities in community affairs, home and hobbies and personal care). The SPC stated the percentage response for the intent to treat population. The response to placebo was 10%, 5mg Aricept had a response of 18% and 10mg Aricept had a response of 21%. Aricept produced a dose-dependent statistically significant increase in the percentage of patients who were judged treatment responders.

The changes in the SPC were as a result of the mutual recognition procedure.

The Appeal Board noted the submission from the companies that the advertising was consistent with changes in cognition. The Appeal Board's view was that the combination of the photograph of the mother and daughter and the wording "but she knew I was calling today" gave the impression that the patient's memory improved following treatment with Aricept.

The Appeal Board examined the data supplied by the companies. It accepted that the area was a difficult one. The Appeal Board noted that ADAS-cog was a scale used to assess the severity of selected areas of cognitive impairment (memory, language, orientation, reason and praxis). The Appeal Board noted the submission that untreated patients with moderately severe disease showed cognitive decline of 7 to 11 points per year. Patients with mild disease or severe disease declined at a slower rate of 4 to 5 points a year. The Appeal Board noted the companies' submission that an improvement of 4 points was a clinically significant effect. The data in Study 302 showed that an improvement of four points or greater in ADAS-cog score versus baseline was seen in 26.8% of placebo treated patients, 37.8% of 5mg/day

donepezil treated patients and 53.5% of the 10mg/day donepezil treated patients. Improvement of seven points or greater versus baseline at study endpoint was seen in 25.2% of the 10mg donepezil group, 15.4% of the 5mg donepezil group and 7.8% of the placebo group.

The Appeal Board noted that the data showed that the decline of cognitive function in patients with Alzheimer's was slowed following treatment with Aricept compared to treatment with placebo. Memory was only one of the elements of cognitive function. It had not been studied separately. A change in cognitive function could be due to elements other than memory. The Appeal Board accepted that there were some patients who might experience an improvement in cognitive function. There was however insufficient data to support the impression given by the advertisement that memory in particular improved following treatment with Aricept. The advertising was not a balanced view of the data. The Appeal Board therefore ruled a breach of Clause 7.2 of the Code.

The appeal was therefore successful.

CASES AUTH/659/12/97 & AUTH/660/12/97

A letter in the British Medical Journal, 13 December 1997, from a senior lecturer at a London hospital criticised the promotion of Aricept. In accordance with established procedure the matter was taken up and dealt with as a complaint under the Code.

COMPLAINT

The author of the letter stated that the caption in the advertisement "Mum has Alzheimer's but she knew I was calling today" was a powerful claim for efficacy in a condition currently believed to be incurable and relentlessly progressive.

The author referred to the three references cited in the advertisement to support the claim. These included two to data on file and one to a published randomised trial in which small, short term changes were observed on a single subscale of wider mental state assessment. Groups contained up to forty patients each and the significance was at the p=0.04 level. Confidence intervals were not given.

The author stated that given the number of other instruments used in the trial it was highly likely that the differences attributed to the intervention could have arisen by chance. An independent review of this study and the unpublished data stated that two other randomised trials comparing donepezil with placebo, which had not been published, had shown smaller differences between intervention and control groups.

The author concluded by stating that perhaps the manufacturers could provide more convincing evidence of efficacy as a condition for retaining prominent advertising on the inside back cover of the British Medical Journal.

* * * * *

The Authority noted that the allegations made in the letter were similar to those made in two complaints already dealt with by the Authority, Cases AUTH/561/5/97 & AUTH/562/5/97, as already set out in detail above, and also Cases AUTH/593/8/97 & AUTH/594/8/97, dealt with below, in all of which the Panel had ruled no breach of the Code.

Eisai and Pfizer had agreed with the Authority that this matter (Cases AUTH/659/12/97 & AUTH/660/12/97) was similar to the previous complaints and that the responses in Cases AUTH/561/5/97 & AUTH/562/5/97 and Cases AUTH/593/8/97 & AUTH/594/8/97 would apply to the new cases.

Previously decided Cases AUTH/593/8/97 & AUTH/594/8/97

The complainant in these cases alleged that it was misleading to imply that the mother had improved sufficiently to restore her memory when the research trials had failed to establish clearly this sort of clinical improvement.

RESPONSE

Eisai had submitted on behalf of both companies that the complainant was mistaken in suggesting that the picture implied a recovery of the memory of the mother. It depicted a daughter who was pleased that her mother's condition had been improved by her new medication. This was a natural and self evident reaction and did not in the company's opinion require substantiation beyond that of the licensed indication for the product. It was unreasonable to infer that this picture correlated with a specific type of improvement or degree of effect.

The principal claim implied by the mailing was the improvement in cognitive function of the patient although the complainant, the company believed mistakenly, considered that it had a more wide ranging message. It was suggested that the mailing claimed an improvement in "clinical outcome" but the complainant did not define what was meant by "outcome". The complainant stated that the licence was based upon clinical effectiveness of the medicine over placebo and only one out of three research studies had been subject to standard peer review in a medical journal.

Eisai referred to the Aricept SPC, pivotal studies 301 and 302 and responder analyses undertaken for regulatory bodies. Reference was made to the draft guidelines for antidementia medicinal products produced by the CPMP working party on efficacy of medicinal products. Copies of these documents and the US product information were provided.

The claims made or implied in the mailing were consistent with the SPC. Aricept was indicated for the symptomatic treatment of mild or moderate dementia in Alzheimer's disease. The claims made in the mailing were consistent with this indication.

The section in the SPC headed "Pharmacodynamic properties" stated that significant correlation was demonstrated between plasma levels of donepezil hydrochloride, AChE inhibition and change in ADAS cog (Alzheimer's Disease Assessment Scale, cognitive subscale) a sensitive scale which examined memory. The section headed "Pharmacokinetic/dynamic properties - characteristics in patients" stated that in two double blind randomised trials, statistically significant drug placebo

differences were present for each of two primary outcome measures (ADAS cog/CIBIC plus) (Clinician's Interview - Based Impression of Change - Plus Version).

Eisai submitted that the claims made for improved cognition and global function were supported by the SPC.

With respect to the comment that the data had not been subject to standard peer review, Eisai pointed out that studies 301 and 302 had been under review by publishing bodies and 302 had been accepted for publication. However, regardless of that fact the company was concerned about the complainant's misconception that peer reviewed journals applied a more robust assessment of a product's efficacy and clinical application than the regulatory review to which all medicinal products were subject. A positive decision to grant a marketing authorisation for Aricept had been made by the regulatory authorities in the US and 14 European countries.

In response to the comment that the clinical effectiveness of Aricept was marginal and not useful, the company drew attention to the CPMP draft guidelines on the antidementia medicinal products issued by the European Medicines Evaluation Agency. This document recommended that measures of cognition, global function and activities of daily living should be used to assess efficacy. Studies 301 and 302 demonstrated clinical effectiveness and usefulness and thus satisfied the criteria set in the guidelines.

Eisai submitted that ADAS cog and CIBIC plus were scales widely used to measure cognition and global function in studies of Alzheimer's disease. Both studies showed statistically significant differences between Aricept and placebo. In addition they showed a disappearance of this efficacy over the placebo washout phase of the study during which the patient remained blinded to the treatment.

Activity in daily living data had been derived from the CDR SB (Clinical Dementia Rating - Sum of the Boxes) domains from study 302. The data had been presented at the American Academy of Neurology and the abstract was provided. These data showed that treatment with 10mg Aricept resulted in a delay in the time to a significant reduction in the activities of daily living. Responder analyses had been requested by several regulatory authorities, an example being the responder groups with respect to different levels of cognition found in the US product information. A new SPC would soon replace the current one and was consequent upon the mutual recognition procedure. The new SPC would include a responder analysis based upon a greater than 4 point increase in the ADAS cog scale plus stabilisation or improvement of global function and activities of daily living. This exacting analysis showed a statistically significant drug effect and in the company's opinion showed that Aricept would provide benefit over and above simple cognitive enhancement in a minority of patients suffering Alzheimer's disease.

Eisai submitted that the data referred to above supported the mailing and therefore that it was not in breach of Clause 7.2 or 7.3 of the Code of Practice.

PANEL RULING

The Panel noted its ruling in the previous cases, Cases AUTH/593/8/97 & AUTH/594/8/97.

Previous Ruling in Cases AUTH/593/8/97 & AUTH/594/8/97

In Cases AUTH/593/8/97 & AUTH/594/8/97 the Panel had noted that the complaint had much in common with Cases AUTH/561/5/97 & AUTH/562/5/97 although they were not entirely at one and Cases AUTH/593/8/97 & AUTH/594/8/97 had therefore been treated as a fresh matter.

The Panel noted the complainant's point that only one of the three research trials had been published and subjected to standard peer review in a medical journal. The Panel noted the submission from Eisai that data from study 302 had now been accepted for publication. Aricept was a relatively new medicine and in the Panel's view it was not unusual for there to be few clinical papers published at this stage. More data than existed in the public domain would have been submitted to, and scrutinised by, the licensing authorities. The Panel noted Eisai's submission that ADAS cog and CIBIC plus were scales widely used to measure cognition and global function in studies of Alzheimer's disease and that studies 301 and 302 had shown statistically significant differences between Aricept and placebo with regard to these scales.

The Panel did not accept the allegation that the advertisement implied that Aricept restored memory. The leaflet referred to Aricept as "A first step in Alzheimer's" and contained the claim that "...patients showed improvement or arrested decline of cognitive symptoms and global function...". The Panel noted that there was data to support an improvement of cognitive function with Aricept and in the face of such improvement the Panel considered that mother and daughter would have cause to look happy. The Panel did not consider that the advertisement was misleading with regard to the efficacy of Aricept, it was not being claimed that the product was a cure for Alzheimer's disease. No breach of Clause 7.2 of the Code was ruled. This ruling applied to both cases.

Panel Ruling in the new Cases AUTH/659/12/97 & AUTH/660/12/97

The Panel considered that its rulings in Cases AUTH/561/5/97 & AUTH/562/5/97 and Cases AUTH/593/8/97 & AUTH/594/8/97 would also apply to the complaint now before it. The Panel therefore ruled no breach of Clauses 7.2 and 7.3 of the Code.

APPEAL BY THE COMPLAINANT

The complainant, the author of the letter in the British Medical Journal, said that Eisai and Pfizer were putting out full colour, full page advertisements in highly prominent places which were designed to give general practitioners and specialists the impression that Aricept could reliably and predictably make elderly people recognise their relatives on the telephone, when previously their dementia was such that they could not recognise them.

No such efficacy had ever been demonstrated for Aricept

and the complainant's personal feeling was that this advertising was greedy and immoral. Her initial letter to the British Medical Journal was intended as a protest against such a prestigious journal publishing this kind of inflated claim and she was delighted that it had been taken up as an official complaint. Given that the Authority had accorded the letter that status, she requested that the matter be pursued as an appeal.

RESPONSE FROM EISAI AND PFIZER

Responding on behalf of both companies, Eisai said that the complainant was concerned with the size and prominence of the advertisements placed jointly by Eisai and Pfizer. Eisai wanted to make it clear that at no time in the promotion of Aricept had the advertisements placed in any journals been in breach of any of the provisions of Clause 6 of the Code, which indicated the size and form of journal advertisements.

The complainant's second point was that there was no efficacy demonstrated for Aricept and that the advertisement was misleading and that the complainant considered it gave the impression that an elderly person could recognise a relative on the telephone when previously the dementia of the elderly person was such that they could not recognise such a relative.

Eisai believed that the complainant was putting a very narrow construction on the phrase "But she knew I was calling today". Eisai believed that this phrase and the pictures applied to the daughter of the elderly person calling round to see the elderly person. This was indicated by the fact that the two individuals were pictured together.

With reference to the claim that no efficacy had been demonstrated for Aricept, Eisai said that the substance of the complaint was that only one of three clinical studies had been published and that study, plus an independent review undertaken and published in Bandolier, supported her opinion that the "degree of clinical effectiveness was marginal and it was not apparent what this meant in practical terms of clinical outcome or improvement for the patient". The complainant considered that the advertisement quantified the degree of effect of Aricept because it implied that the mother's memory had been totally restored. The letter of appeal did not seem to add substantially to the initial complaint and re-stated that the picture showed a specific degree of change in the mother's memory.

The points made by the complainant concerning the lack of published data were well taken and Eisai appreciated the necessity to publish. This took time and Study 302 was now published in Neurology and Study 301 had been accepted for the May edition of Archives of Internal Medicine. The study to which the complainant referred in her initial letter (Study 201) was a dosing study and Eisai accepted that it would not have received a marketing authorization based upon that study. The Bandolier article which the complainant cited as independent evidence showing that the Aricept data were weak was completely inaccurate.

The advertisement was meant to convey the message that Aricept helped cognition and that the daughter was happy that her mother had gained benefit from the new medicine. The claim "But she knew I was calling today" did in Eisai's opinion concentrate on the issue of cognitive improvements. Both studies (302 and 301) showed statistically significant improvements in drug placebo comparisons. Included in the US package insert was the responder analysis by degree of change in ADAS cog scores.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant advised that she had nothing to add to her previous comments.

APPEAL BOARD RULING

The Appeal Board considered that its ruling in Cases AUTH/651/11/97 & AUTH/652/11/97, given above, also applied in these cases. The Appeal Board therefore ruled a breach of Clause 7.2 of the Code.

The appeal was therefore successful.

Cases AUTH/651/11/97 & AUTH/652/11/97:

Complaint received **25 November 1997**

Cases AUTH/659/12/97 & AUTH/660/12/97:

Proceedings commenced **9 January 1998**

Cases completed **1 June 1998**

CASE AUTH/654/12/97

CONSULTANT PHYSICIAN v WYETH

Promotion of Minocin MR

A consultant physician complained about a Minocin MR mailing which consisted of a "Dear Doctor" letter and a leaflet which had been sent to dermatologists and general practitioners by Wyeth. The "Dear Doctor" letter was headed "5 Suicides and 51 Hospital Admissions from Drug Overdose" and referred to these as resulting from a series of 25,000 acne sufferers attending one centre, describing this as coming as a great shock. The complainant said that without knowing what the incidence of suicide was in a comparable population it was impossible to know whether it came as a great shock. Even if it did, the centre in question recommended the use of minocycline and the figures were therefore entirely consistent with a theory that minocycline drove people to suicide, in the absence of any comparative data to the contrary.

The Panel noted that neither the "Dear Doctor" letter nor a letter in the British Medical Journal to which it was referenced gave any indication of the suicides or overdoses that might be expected in a matched control group and it was not therefore possible to assess the significance of the figures and to know whether they could properly be described as a great shock. The Panel considered the heading was misleading and it was ruled in breach. It was also ruled in breach because it was sensational in nature and failed to recognise the special nature of medicines and the professional standing of the audience to which the material was directed.

The complainant also referred to two phrases which appeared one after the other in the leaflet: "82% Success as first time antibiotic" and "81% Success in oxytetracycline failures". In small print beneath it was stated that success was "measured by patients assessment". Similar claims were made in the letter. The juxtaposition implied that minocycline was better than oxytetracycline but there was no evidence that this was the case and the company had never performed a comparative controlled trial. The Panel did not consider that the juxtaposition of these two claims implied that Minocin was more effective than oxytetracycline *per se*. The presentation was not misleading and no breach was ruled in that regard.

A consultant physician complained about a Minocin MR mailing (ZMIN482/8/97) which consisted of a "Dear Doctor" letter (ZMIN/484/09/97) and leaflet (ZMIN/482/8/97). The mailing had been sent to dermatologists and general practitioners by Wyeth and promoted Minocin MR (minocycline) as a first line treatment of acne. The "Dear Doctor" letter was headed "5 Suicides and 51 Hospital Admissions from Drug Overdose". The letter referred to the statistics regarding suicides and hospital admissions as resulting from a series of 25,000 acne sufferers treated at a centre in the north of England. It referred to the statistic as coming as a great shock.

The leaflet stated that Minocin MR had an "82% Success as first time antibiotic" and an "81% Success in oxytetracycline failures". Similar claims appeared in the "Dear Doctor" letter.

COMPLAINT

The complainant pointed out that the "Dear Doctor" letter stated that there had been 5 suicides amongst a series of 25,000 acne sufferers attending one hospital, and the letter described this as shocking.

The complainant pointed out that the "Dear Doctor" letter gave no indication of the time over which the survey was conducted. No indication of the age structure of the patients was given, though they were presumably young adults in the main. The complainant submitted that without knowing what the incidence of suicide was in a comparable population it was impossible to know whether such statistics did "come as a great shock". The complainant alleged that even if they did, the centre in question, the General Infirmary at Leeds, notoriously recommended the use of minocycline; the figures therefore were entirely consistent with a theory that minocycline drove people to suicide (in the absence of any comparative data to the contrary).

The complainant referred to two phrases which appeared one after the other in the leaflet: "82% Success as first time antibiotic" and "81% Success in oxytetracycline failures". In small print underneath it was stated that this success was "measured by patients assessment". However, the juxtaposition implied that minocycline was better than oxytetracycline, when there was absolutely no evidence that this was the case and the company had never performed a comparative controlled trial.

The complainant alleged that this was a scandalous piece of promotion.

RESPONSE

Wyeth stated that the 5 suicides and 51 hospital admissions from drug overdose were due to depression from acne. Acne was perceived by many clinicians, and the general public, to be a relatively non serious disease. The factual statement in the letter was intended to draw readers' attention to the fact that many acne sufferers endured severe psychological distress due to their acne and thus emphasised their need for effective treatment at initial consultation.

Wyeth submitted that this statement had been used by The Acne Support Group in various communications, and by Professor W J Cunliffe from the Leeds General Infirmary in two letters published in the British Medical Journal (BMJ).

The centre in Leeds used many medicinal treatments for acne. Its series of 25,000 patients were treated with various regimens and to draw the conclusion that minocycline drove people to suicide was pure fantasy.

Wyeth pointed out that the two statements "82% Success as first time antibiotic" and "81% Success in oxytetracycline failures" were taken from a study by Millar E D *et al* published in the British Journal of Clinical

Practice. The statements were factual and referenced.

Wyeth submitted that no comparison with oxytetracycline was made, nor implied. The measurement of "success" was qualified as measured by patient assessment.

Wyeth believed the mailing represented responsible promotion in full compliance with the Code.

PANEL RULING

The Panel noted that the heading on the "Dear Doctor" letter "5 Suicides and 51 Hospital Admissions from Drug Overdose" was referenced to a letter by Cunliffe (1996) published in the BMJ. The letter entitled "Doctors should not change the way they prescribe for acne" referred to a paper and editorial which drew attention to the uncommon hepatitis and lupus erythematosus - like syndrome induced by minocycline. The letter referred to two deaths reported in association with minocycline. It stated that one of the deaths was more likely to be due to an antimalarial and the second death, from pancytopenia, was thought to be a coincidental association. The letter stated that over 26 years the General Infirmary at Leeds had had no deaths among patients taking minocycline but five patients had committed suicide because of depression associated with acne and a further 51 patients had been admitted to hospital with a drug overdose due to depression.

The Panel noted that neither the letter to the BMJ nor the "Dear Doctor" letter gave any indication as to the number of suicides and overdoses that might be expected in a matched control group. It was therefore not possible to assess the significance of the figures in the "Dear Doctor" letter and to know whether they could properly be described as "a great shock". The Panel considered that the heading was misleading and ruled a breach of Clause 7.2 of the Code.

The Panel noted that certain styles of promotion which might be acceptable for general commodity advertising were unacceptable when promoting medicines to health professionals. The Panel considered that the heading of the "Dear Doctor" letter was sensational in nature and failed to recognise the special nature of medicines and the professional standing of the audience to which the material was directed. The Panel ruled a breach of Clause 9.1 of the Code.

With regard to the claims at issue in the leaflet that Minocin had an "82% Success as first time antibiotic" and an "81% Success in oxytetracycline failures" the Panel noted that they were referenced to a study by Millar *et al* (1987). The second claim appeared immediately beneath the first claim. The Panel did not consider that the juxtaposition of these two claims implied that Minocin was more effective than oxytetracycline *per se*. The presentation of the claims was not misleading and the Panel ruled no breach of Clause 7.2 of the Code.

Complaint received **9 December 1997**

Case completed **18 March 1998**

CASE AUTH/655/12/97

GLAXO WELLCOME v BOEHRINGER INGELHEIM

Journal article

Glaxo Wellcome complained about an article entitled "Trends in the management of COPD" which had appeared in ODA News Review, the journal of the Overseas Doctors' Association. Glaxo Wellcome alleged that the failure of the article to acknowledge the fact that it had been written by two doctors from Boehringer Ingelheim breached the Code. It was also alleged that the article was unbalanced, no less than 37% of it being devoted to Boehringer Ingelheim's product Combivent. Glaxo Wellcome alleged that the article was promotional in nature and breached the Code because it should have carried prescribing information for the Boehringer Ingelheim products referred to, Atrovent and Combivent. A further breach of the Code was alleged because of the failure to provide references to quotations from three studies.

The Panel ruled that the Code had been breached because of the absence of any indication that the article had been written by doctors from Boehringer Ingelheim's medical division, notwithstanding the fact that this omission had been an error and that an erratum statement had subsequently been published. The article had been published with the agreement of Boehringer Ingelheim and it had to take responsibility. In the Panel's opinion readers would assume that the article had been written independently but its content and the fact that it had been written by company employees meant that it was an advertisement for Atrovent and Combivent. Breaches of the Code were ruled as it was disguised promotion and it lacked prescribing information for the products. A further breach was ruled as the Panel considered that the article was not a balanced and up-to-date review of the therapy area. No breach was ruled in relation to the absence of references as the article had not used the phrase "in a published study" or similar, or referred to authors by name.

Glaxo Wellcome UK Limited complained about an article which had been published in the ODA News Review, journal of the Overseas Doctors' Association, in June 1997. The article was entitled "Trends in the management of COPD".

COMPLAINT

Glaxo Wellcome noted that the article had been written by Drs S E Libretto and E Arbe who were both members of the medical division of Boehringer Ingelheim Limited. As the article, which related to the use of medicines in the management of chronic obstructive pulmonary disease (COPD), did not acknowledge this fact Glaxo Wellcome alleged that it was in breach of Clause 9.9 of the Code.

Glaxo Wellcome stated that the article was apparently written at the request of the editor of the ODA News Review who required a scientific article on COPD and its treatment. However, Glaxo Wellcome considered that only just over half of the article could be viewed as balanced - no less than 37% of the article was devoted to Boehringer Ingelheim's product Combivent (ipratropium and salbutamol) and the description of the results of clinical trials involving this product. There was a clear statement that the optimal treatment schedule for a combination of the individual components of Combivent was for fixed doses to be taken every 6 hours. It was claimed that one of the studies quoted showed that Combivent was both more effective and longer acting than either of its individual components. Glaxo Wellcome considered that the article was promotional and, as it contained no prescribing information for either Atrovent (ipratropium) or Combivent (both Boehringer Ingelheim's products), alleged that it was in breach of Clause 4.1 of the Code. In view of the absence of any attribution of origin on this promotional item it was disguised promotion in breach of Clause 10.1 of the Code.

Glaxo Wellcome noted that the article quoted data and conclusions from three studies, one involving Atrovent and two concerning Combivent. The article did not give any references for these studies and so Glaxo Wellcome alleged a breach of Clause 7.5 of the Code.

Glaxo Wellcome stated that the title of the article suggested that it addressed new directions in the management of COPD. Glaxo Wellcome pointed out, however, that Combivent had ten mentions by name but there was no reference at all to the possible place of salmeterol (Glaxo Wellcome's product Serevent) in the management of COPD. Serevent was granted a licence for its use in COPD in July 1996. Two major papers regarding its use had been published in April 1997 (Boyd *et al* and Jones and Bosh) which provided evidence for its role in COPD. The data from both papers had also been presented at international meetings of the American Thoracic Society and the European Respiratory Society in 1995, and so were in the public domain. Glaxo Wellcome alleged that in view of this the article was not balanced, fair or objective in breach of Clause 7.2 of the Code.

RESPONSE

Boehringer Ingelheim acknowledged that the authors, Drs Libretto and Arbe, were both member of the company's medical division and that such attribution should have been made clear in the article. The editor of the ODA News Review had confirmed that he had requested the article and that it was his error that his usual practice of publishing the affiliation of the authors had, in this instance, been omitted. Boehringer Ingelheim provided an erratum statement, published in the November/December 1997 issue of the journal, which made the affiliation of Drs Libretto and Arbe clear. In these circumstances, Boehringer Ingelheim considered that it would be unreasonable to rule a breach of Clause 9.9 of the Code.

Boehringer Ingelheim noted that Glaxo Wellcome had complained that the article was not balanced, fair or objective as the section concerned with therapy concentrated on the use of short-acting ß-agonists and anticholinergics, separately and combined, and did not refer to the use of the recently licensed Glaxo Wellcome long-acting ß-agonist, salmeterol.

Boehringer Ingelheim stated that in 1997 the British

Thoracic Society (BTS) had published Guidelines for the Management of Chronic Obstructive Pulmonary Disease and that under the heading "Bronchodilator therapy at each stage of COPD" there were recommendations for treatment of patients with mild, moderate or severe disease. Patients with symptoms and mild disease were recommended to receive an inhaled (short-acting) ß-agonist or anticholinergic taken as required. Patients with moderate disease should receive a single short-acting ß-agonist or anticholinergic but a few would need a combination of them. For patients with severe disease it was stated that "Most will justify combination of $ß_2$-agonist and anticholinergic if they derive increased benefit from this combination".

Boehringer Ingelheim stated that with respect to long-acting $ß_2$-agonists the BTS Guidelines stated the following: "There is only limited evidence on the efficacy of long acting $ß_2$ agonists in COPD. Until more data are available their use should be limited to patients with a demonstrable bronchodilator response to $ß_2$ agonists and their use monitored by assessment of both symptoms and FEV_1".

Boehringer Ingelheim stated that it was clear from the BTS Guidelines that short-acting ß-agonists and anticholinergics, either separately or combined, were the mainstay of therapy in COPD, and that the place of long-acting ß-agonists, such as salmeterol, had yet to be determined. The absence of reference to long-acting ß-agonists was in accord with the conclusion of the BTS Guidelines on this type of product.

Boehringer Ingelheim submitted that the article by Libretto and Arbe was entirely consistent with the BTS Guidelines and gave a similar emphasis to the use of short-acting ß-agonists and anticholinergics administered separately or combined. As befitted a scientific paper, the article provided the clinical evidence on which the use of these agents was based.

Boehringer Ingelheim stated that the article did not constitute promotion, overt or disguised. The article was a fair presentation of current knowledge on the use of bronchodilator products in the treatment of COPD and so was not in breach of Clause 7.2 of the Code. Boehringer Ingelheim also denied breaches of Clauses 4.1, 7.5 and 10.1 of the Code.

PANEL RULING

The Panel noted that the article in question had been written by two members of Boehringer Ingelheim's medical division but that there was no declaration to this effect. The Panel noted Boehringer Ingelheim's submission that this was an omission on the part of the editor of the ODA News Review and that an erratum had been published. The Panel noted that the article was produced with the agreement of Boehringer Ingelheim. The company was therefore responsible under the Code.

The Panel noted that the article was just over one page (A4) long and was entitled "Trends in the Management of COPD". The first part explained the burden of COPD with particular reference to NHS costs with the remaining two thirds of the article detailing clinical trials with Atrovent and Combivent. The Panel noted that there were ten mentions of the product name Combivent and one of Atrovent. In the opinion of the Panel a reader would assume that the article had been written independently but the content and the fact that it had been written by company employees meant that it was an advertisement for Atrovent and Combivent. The Panel considered that the article thus constituted disguised promotion in breach of Clause 10.1 of the Code.

The Panel noted that the promotional nature of the article meant that prescribing information for Atrovent and Combivent was needed. There was no prescribing information for either product included in the article in breach of Clause 4.1 of the Code. The Panel ruled accordingly.

The Panel noted that Clause 7.5 of the Code stated that when promotional material referred to published studies clear references must be given. The Panel considered that Clause 7.5 meant that if promotional material used the phrase "in a published study" or similar, then references needed to be given. The Panel further considered that if promotional material referred to the author or authors of published studies by name, then this amounted to referring to a published study and references should be given. The Panel noted that the article in question referred to a number of studies for Atrovent and Combivent. No authors, dates or publication details were given. The Panel had no way of knowing if the studies referred to had been published or were data on file. The article had not used the phrase "in a published study" or similar nor had it referred to authors by name. The Panel decided that in the circumstances there was no need to give references and ruled no breach of Clause 7.5 of the Code.

The Panel noted that the article discussed the treatment of COPD only in terms of Atrovent and Combivent. No other treatment options were mentioned. The Panel noted that the article had appeared in the June 1997 issue of the ODA News Review. Serevent had been licensed for use in COPD since July 1996 and data regarding such use had been in the public domain since 1995, at least in the form of conference abstracts, with two full papers being published in April 1997. In the Panel's view the authors of the article would have been aware of the use of Serevent for COPD when they wrote the article. The title of the article "Trends in management of COPD" suggested that it was a review of all management options in COPD which was not the case. The Panel considered that the article was not a balanced or up-to-date review of the therapy area and ruled a breach of Clause 7.2 of the Code.

The Panel considered that the failure to identify the authors of the article as employees of the company amounted to a breach of Clause 9.9. The Panel therefore ruled a breach of that clause.

Complaint received **12 December 1997**

Case completed **16 April 1998**

CASE AUTH/656/12/97

DIRECTOR/MEDIA v BAYER

Adalat advertisement

A letter published in the British Medical Journal critical of a journal advertisement for Adalat (nifedipine) issued by Bayer was taken up as a complaint under the Code. The advertisement detailed results from the recently published STONE study. The letter referred to a statement in the advertisement "This prospective placebo-controlled clinical intervention trial has demonstrated for the first time a significant reduction in severe clinical outcomes with the dihydropyridine nifedipine." which was in fact the last sentence of the published paper. The shortcomings of the study had been pointed out in the introduction to the paper in which the authors stated that "It is our belief, however, that, within the stated restrictions, the study design and execution warrant publication of the results in an international medical journal". The authors also stated that "Because of its unorthodox design (single-blinded sequential assignment with transfer of severely hypertensive subjects from placebo to the active-treatment group), we decided to approach the data via different types of analysis to limit overinterpretation bias.". The letter stated that readers of the advertisement were not aware of the shortcomings of the study on which it was based and thus would suppose that it concerned a prominent clinical study which might have clinical implications.

The Panel noted that the heading, statement and table in the advertisement were each referenced to the STONE study, which was a single-blind controlled trial of nifedipine and placebo in 1,632 hypertensive patients aged 60-79 in China. Of the cardiovascular events measured, only strokes and severe arrhythmia achieved a statistically significant outcome. The authors of the study accepted that its design and single-blinded conduct were limitations on the study, particularly with regard to the size of the obtained benefit. The Panel noted that no reference had been made in the advertisement to the ethnic origin or age of the population. Given the reservations about the methodology, the Panel considered that the statement at issue was not a balanced reflection of the study. Overall the Panel considered that the results had been presented in a misleading fashion and a breach was ruled. A further breach was ruled because, while the authors of the study had discussed its strengths and weaknesses, the use of only a positive quotation in the advertisement misrepresented their views. The authors' reservations had not been conveyed.

A letter in the British Medical Journal (BMJ) of 13 December 1997 from a general practitioner criticised an advertisement for Adalat (nifedipine) issued by Bayer which had appeared in the BMJ of 12 April 1997. In accordance with established procedure the criticisms were taken up and dealt with as a complaint under the Code.

The advertisement in question was headed "Research for the future STONE STUDY", beneath which it stated "This prospective placebo-controlled clinical intervention trial has demonstrated for the first time a significant reduction in severe clinical outcomes with the dihydropyridine nifedipine.". Both the heading and statement were referenced to the STONE study (Gong *et al*: Shanghai trial of nifedipine in the elderly (1996)). Beneath the statement was a table showing the reductions in outcomes demonstrated by the STONE study.

The letter criticised the advertisement for its failure to mention shortcomings of the STONE study. Beneath the letter in question the BMJ published a response from Leighton and Telford of Bayer plc Pharmaceutical Division and a response from Dr Pavel Hamet, one of the authors of the STONE study.

COMPLAINT

The author referred to the statement "This prospective placebo-controlled clinical intervention trial has demonstrated for the first time a significant reduction in severe clinical outcomes with the dihydropyridine nifedipine." which was the last sentence of the published paper. The author pointed out that the shortcomings of the study were mentioned in the introduction to the study which stated that "It is our belief that within the stated restrictions, the study design and execution warrant publication of the results in an international journal". The study also stated that "Because of its unorthodox design (single-blinded sequential assignment with transfer of severely hypertensive subjects from placebo to the active-treatment group) we decided to approach data via different types of analysis to limit overinterpretation bias.".

The author stated that readers of the advertisement were not aware of the shortcomings on which it was based and they would thus suppose that it concerned a prominent clinical study which might have consequences in clinical practice; in this instance, the adjustment of treatment in patients with moderate hypertension. The BMJ strongly advocated controlled clinical trials and was dismissive of attempts to use statistical fireworks to overcome a study's shortcomings. The author presumed it would agree that, according to its own criteria, nothing was shown by the publication cited in the advertisement.

In the author's view the BMJ should make clear to its readers that, currently, scientifically founded data on the treatment of hypertension was available only for thiazide diuretics and beta-blockers and that the effects of using calcium entry blockers were still unknown. In the editor's footnote to recent letters about advertisements in the BMJ, the editor wrote that the journal rarely rejected advertising material on the grounds of unsubstantiated or misleading claims. The author thought that the advertising policy should be changed. The references that were used in advertisements should be checked for their scientific relevance.

RESPONSE

Bayer plc Pharmaceutical Division submitted that in relation to Clause 7.2 of the Code, the information presented in the advertisement was entirely accurate, fair, objective and unambiguous and was based on an up-to-date evaluation of all the evidence available at the time on the effect of nifedipine on outcomes in elderly hypertensives and reflected the evidence clearly. The

statements did not mislead either indirectly or by implication. On the contrary, the advertisement highlighted an important study which showed for the first time the beneficial effects on outcomes of nifedipine in this group of patients and as such was of great importance to medical practitioners who required up-to-date information relevant to the treatment of these patients. Bayer pointed out that prior to the publication of this study the only trials showing a benefit on outcomes were those which used a thiazide diuretic or a beta-blocker. Since the STONE study was published the results of the SYST-EUR trial had become available which also showed a reduction in outcomes with the dihydropyridine calcium antagonist nitrendipine (Staessen *et al*, Systolic Hypertension in Europe; Lancet (1997)).

Bayer stated that it was entirely right for it to bring these important landmark studies to the attention of medical practitioners. It would always provide copies of these studies to practitioners through its medical information department (in accordance with Clause 13 of the Code), in order that they were able to assimilate the information and formulate their own opinions. Bayer referred to the letter published in the BMJ from Leighton and Telford.

Bayer did not believe that it was in breach of Clause 7.2 of the Code, and in this respect submitted that it had acted in a right and proper manner.

Bayer stated that the information given in the advertisement was properly referenced and therefore was fully substantiated. Bayer submitted that it was not in breach of Clause 7.3.

Bayer stated that the quotation used in the advertisement clearly and accurately reflected the meaning of the author. Dr Hamet had, in his letter to the BMJ, clearly stated that both the shortcomings and positive points of the trial were fully discussed in the STONE publication. In fact the publication concluded that "... this prospective placebo-controlled clinical intervention trial has demonstrated for the first time a significant reduction in severe clinical outcomes with the dihydropyridine nifedipine". Dr Hamet stated in his letter that the design of the study was similar to that of the Veterans Administration study, a "landmark study" which showed for the first time that "hypertension treatment is worthwhile". Dr Hamet stated that the STONE study was also a landmark study, giving doctors the opportunity to rely on newer classes of medicine. Bayer stated that Dr Hamet's letter clearly reflected his current opinions and therefore it submitted that it was not in any way in breach of Clause 11.2 of the Code.

Finally, Bayer referred to the letters of response published in the BMJ of 13 December which pointed out that the final paragraph of the letter of complaint was simply inaccurate. Scientifically founded information on the treatment of hypertension was available not only for thiazide diuretics and beta-blockers but now also for the dihydropyridine calcium antagonists, nifedipine and nitrendipine.

PANEL RULING

The Panel noted that the heading, statement and table were each referenced to the STONE study. The STONE study was a single-blind controlled trial of nifedipine and placebo in 1,632 elderly hypertensive patients (aged 60-79) in China. The primary hypothesis was to determine the difference in the number of cardiovascular events between the two patient groups. The study showed that of those cardiovascular events measured, only strokes and severe arrhythmia achieved a statistically significant outcome.

The authors of the study referred to the study's unorthodox design. The study was single-blinded with sequential assignment to nifedipine or placebo. Seventy four patients with severe hypertension were reallocated to active treatment after the placebo run-in period. Initial assignment into placebo and active groups was not strictly randomised. The authors of the study accepted that its design and single-blinded conduct were limitations of the study, particularly with regard to the size of the obtained benefit. The Panel noted that analysis was undertaken in Canada to ascertain the validity of the results.

The Panel noted that the patient population was Chinese, aged between 60 and 79 years of whom 95% were from the Hon ethnic group. The study stressed that the Chinese population studied appeared to have predictors of clinical events (other than myocardial infarction) similar to those of other ethnic groups, including the Framingham population and other Caucasians. The study stated that it had been demonstrated that myocardial infarction was much less frequent than were strokes in the People's Republic of China and thus no conclusion could be drawn regarding this relatively rare event in the Chinese. The Panel considered the ethnic origin of the patient population might be relevant to the audience. The Panel noted that the advertisement made no reference to either the ethnic origin or age of the patient population.

Given the reservations about the study methodology the Panel considered that the statement at issue "This prospective placebo-controlled clinical intervention trial has demonstrated for the first time a significant reduction in severe clinical outcomes with the dihydropyridine nifedipine" was not a balanced reflection of the study. The table showed reductions in clinical outcomes but did not give any information about the statistical significance. Overall the Panel considered that the results had been presented in a misleading fashion and therefore ruled a breach of Clause 7.2 of the Code.

The Panel considered that in view of its ruling of a breach of Clause 7.2 of the Code there was no need to consider whether or not there had been a breach Clause 7.3 of the Code.

Clause 11.2 of the Code required that "Quotations from medical and scientific literature ... must accurately reflect the meaning of the author". The Panel noted that care should be taken to ensure that such quotations did not mislead as to their overall significance. The Panel considered that whilst the authors of the study had openly discussed the study's strengths and weaknesses, the use of only a positive quotation in the advertisement misrepresented their views. The author's reservations about the study design had not been conveyed. The Panel considered that the quotation used did not wholly reflect the opinions of the authors and thus unduly emphasised the significance of the study results. A breach of Clause 11.2 was ruled.

Proceedings commenced **16 December 1997**

Case completed **1 April 1998**

CASE AUTH/657/12/97

PARKE DAVIS v MERCK SHARP & DOHME

Zocor medical information letter

Parke Davis complained about a twelve page medical information letter sent to a pharmacist by Merck Sharp & Dohme. The letter began "Thank you for your enquiry concerning a comparison of Zocor (simvastatin - MSD) with the other statins.". The letter went on to compare Zocor with four other statins, the first being atorvastatin (Lipitor, Parke Davis).

It was alleged that the letter was both promotional and misleading. A summary of the 4S study (Scandinavian Simvastatin Survival Study) had been included in the comparison to atorvastatin section but this was not a comparative study and it was alleged that its inclusion fell beyond the scope of a comparative efficacy enquiry. A sentence, in bold type, which drew attention to the fact that atorvastatin had no endpoint in primary and secondary prevention trials was alleged to be overtly promotional. The summary section of the comparison with atorvastatin contained what amounted to three promotional stabpoints. The comparison between simvastatin and atorvastatin was alleged to be ambiguous and misleading. It was alleged that the letter deliberately misled the reader and disparaged atorvastatin and the opinions of the authors involved. Prescribing information for Zocor had not been provided, there were no directions as to where to find it and the date of preparation had not been included.

The Panel noted that the term promotion did not include replies made in response to individual enquiries from members of the health professions if these related solely to the subject matter of the enquiry and were not promotional in nature, but considered that the letter fell outside this exception. It was not an unbiased discussion of the effect of Zocor alone or in comparison with other statins. The name Zocor always appeared in capitals and criticisms of atorvastatin were presented in a prominent manner. The letter was promotional and subject to the Code.

The letter should have included prescribing information and a reference to where it could be found. Both were missing and breaches were ruled in both respects. There was no breach relating to the lack of a date of preparation because the date of the letter constituted the date on which it was prepared. The Panel considered that while it had been appropriate to include the 4S study data in the letter it was inappropriate and misleading to include the details in a section comparing Zocor and atorvastatin and a breach was ruled in that regard. In addition, the Panel considered that the statement regarding the lack of studies on atorvastatin and CHD, although true, was misleading given that the product was not licensed for use in CHD and a further breach was ruled. In relation to the casting of doubt upon the validity of two trials in hypercholesterolaemia by stating that the doses of Zocor and atorvastatin which had been compared were not equipotent, the Panel noted that the doses had been those licensed in hypercholesterolaemia. The Panel considered that the statements disparaged atorvastatin and they were ruled in breach. The Panel did not consider that the statements amounted to disparagement of the opinions of the various authors and ruled no breach in that regard.

Parke Davis & Co Limited complained about a twelve page medical information letter sent to a pharmacist by Merck Sharp & Dohme Limited. The letter was headed "Zocor: Comparison with other statins". The letter began "Thank you for your enquiry concerning a comparison of Zocor (simvastatin - MSD) with the other statins". The letter went on to compare Zocor with four other statins the first being atorvastatin (Lipitor, Parke Davis). There was nothing on the letter to identify to whom it had been sent.

Consideration of this case was delayed as Merck Sharp & Dohme stated that it was not able to respond adequately to the complaint without knowing what information had originally been requested by the pharmacist. Parke Davis took over a month to respond to Merck Sharp & Dohme's request for further information. The reason for the delay was that it took some time for the pharmacist to write to Parke Davis. Parke Davis then provided, in confidence to the Authority, a letter from the pharmacist in which he stated that he had "... telephoned MSD and other manufacturers of HMG CoA reductase inhibitors requesting information regarding "head to head" comparisons with other HMG CoA reductase inhibitors, and trial data that revealed the effect of their drug against the various lipid parameters (eg percentage LDL reduction.)".

COMPLAINT

Parke Davis alleged that the letter was promotional in nature and content and was misleading. It failed to adequately address the comparative efficacy data for the different available statins and instead took the opportunity to promote simvastatin. Parke Davis alleged breaches of Clauses 1.2, 4.6, 4.7, 7.2, 8.1 and 8.2 of the Code.

Clause 1.2 of the Code stated that the term "promotion" did not include replies made in response to individual enquiries from members of the health professions but only if they related solely to the subject matter of the letter or enquiry and were not promotional in nature. This letter was clearly promotional in nature and content due to the following:

A summary of the 4S study was included within the comparison to atorvastatin section. The 4S study was not a comparative study and therefore its inclusion fell beyond the scope of a comparative efficacy enquiry. It was clearly included to promote simvastatin in coronary heart disease (CHD) reduction. Its use within the comparison to atorvastatin was irrelevant and wholly inappropriate to an enquiry of this kind.

On page 3 of the letter the first sentence under the headline "Effect On CHD", which drew attention to the fact that atorvastatin had no endpoint data in primary and secondary prevention trials, was in bold type. This bold type was clearly designed to stand out to the reader and was overtly promotional in style. There were no endpoint studies directly comparing statins in primary or secondary prevention. Such reference to endpoint data in

this context was again irrelevant.

The summary section of the comparison with atorvastatin contained what amounted to three promotional "stabpoints" for simvastatin. The brand name "Zocor" was in each sentence in capital letters and each sentence contained no mention of atorvastatin. This was again clearly overtly promotional in style and Parke Davis argued was contrary to the exclusion under Clause 1.2 of the Code.

As a promotional piece the item was in breach of Clauses 4.1, 4.6 and 4.7. Prescribing information for simvastatin was not provided, there were no directions on page 1 referring the reader to prescribing information, and the date that the material was drawn up or last revised was not included. The date of the letter did not indicate when the item was prepared, merely when it was sent to the enquirer.

The comparison between simvastatin and atorvastatin as described in this promotional item was ambiguous and misleading to the reader, thus breaching Clause 7.2 of the Code. The supplementary information to the Code stated that comparisons of potency were generally meaningless and best avoided unless they could be linked with some practical advantage, for example a reduction of either side effects or the cost of effective dosage. The letter, however, contained a number of inappropriate references to scientific articles and attempted to confuse the reader by raising the issue of potency. For example:

The opening paragraph on page 2 of the letter, when introducing the comparative studies involving simvastatin and atorvastatin, stated that, "When drawing conclusions from the following studies it should be borne in mind that the relative potency has not been confirmed in large scale trials; therefore the studies may not look at comparable dosages".

The fourth paragraph on page 2, describing the study by Heinonen *et al*, showed the superior efficacy of atorvastatin in reducing cholesterol, LDL-cholesterol and triglycerides, but then misled and confused the reader by stating that "These results are not unexpected as the doses used were not equipotent". The study was of comparative efficacy and it demonstrated a clear answer to the question but this was not reflected in the letter from Merck Sharp & Dohme.

Similarly in paragraph 5, summarising the trial by Best *et al*, the letter stated "By analysis of covariance the effects on total cholesterol and LDL-cholesterol were significantly greater for atorvastatin, which would not be unexpected as non-equipotent doses were compared".

The opening sentence on page three of the letter stated "Further head-to-head studies using equipotent doses are clearly needed to compare the long-term efficacy and safety of atorvastatin with simvastatin". This sentence was in bold type seemingly trying to lend weight to it in the reader's eyes.

The repeated use of statements claiming that equipotent doses needed to be compared was misleading, ambiguous and irrelevant. Atorvastatin and simvastatin were not equipotent drugs. 10mg of atorvastatin had the same effect on lipid values as 20-30mg of simvastatin, ie atorvastatin was 2-3 times as potent as simvastatin. However, potency was not the issue. The patient and the prescribing doctor were interested in efficacy, and Merck Sharp & Dohme was trying to say, or imply, that equi-effective doses should be compared, ie 10mg atorvastatin and 20-30mg of simvastatin. By definition, the effect of these doses on lipid values would be the same, but the dose, and cost, of atorvastatin was substantially less. Merck Sharp & Dohme's argument was meaningless and it had not responded to the challenge of explaining exactly what it meant. The Authority had recently ruled on the issue of potency in the promotion of cerivastatin (Case AUTH/567/6/97).

Atorvastatin and simvastatin were of comparable cost at comparable milligram doses and all data available suggested a similar profile. It was the efficacy within the dose range licensed for use by the prescriber that was of relevance when comparing pharmaceutical products. Clinicians would prescribe a statin at its lowest dose and titrate upwards until patients achieved their LDL-cholesterol target according to local, national, or international guidelines. The important point here was how much cholesterol reduction was achieved within the licensed dose range of the statin.

By repeatedly implying that the trial data listed in the comparison with atorvastatin were of questionable relevance, due to the fact that equipotent doses were not used, the item deliberately misled the reader and, therefore, cast aspersions on atorvastatin in an attempt to derive commercial advantage. This constituted a breach of Clause 8.1 of the Code as it was disparaging to atorvastatin. Parke Davis also believed this breached Clause 8.2 of the Code by implying that the comparative trials referenced in the comparison were poorly designed and of little relevance.

RESPONSE

Merck Sharp & Dohme said that the medical information letter was sent in response to a specific enquiry by a pharmacist and contained the information that had been requested. After receiving the enquiry, the medical information officer selected appropriate data from a range of well researched standard responses, searched the electronic databases for new information and summarised this data to prepare an individual response. The date on which this letter was sent was the date it was prepared.

The information the pharmacist requested was on 'head to head' comparisons with other HMG CoA reductase inhibitors and trial data that revealed the effect of Merck Sharp & Dohme's product (in this case simvastatin) against the various lipid parameters (eg percentage LDL reduction).

The medical information letter had sections on atorvastatin, pravastatin, fluvastatin and cerivastatin but the complaint related only to the section on atorvastatin. Merck Sharp & Dohme would refer only to this section.

The letter compared the licensed indications, described the comparative studies of atorvastatin and simvastatin, and included a non-comparative section on the known effects of the two drugs on CHD (coronary heart disease), in diabetics, effects on triglycerides and long term tolerability data. At the time this letter was sent there were relatively few head to head comparisons of atorvastatin and simvastatin and these studies were very

short term. In order to present a meaningful comparison of the efficacy of the two drugs, it was necessary to include non-comparative studies. Nearly all of the published data was from very small studies or just in preliminary abstract form. Merck Sharp & Dohme believed it was generally accepted that data from very small studies must always be viewed with caution, as should data from abstracts.

The studies described for atorvastatin were representative of the published data at that time, and the study used to illustrate the efficacy of simvastatin was the 4S (Scandinavian Simvastatin Survival Study) which was the largest and longest study of simvastatin in the treatment of hypercholesterolaemia.

As the letter was rather long, bold type and spaces were used to break up the sections of data but after recent review this format was no longer used. They were not intended to be used for any other emphasis or effect.

Merck Sharp & Dohme responded to each individual complaint made by Parke Davis.

1 Complaint: A summary of the Scandinavian Simvastatin Survival Study was included

The pharmacist requested "... and trial data that revealed the effect of their drug against the various lipid parameters (eg percentage LDL reduction)". He did not just ask for comparative data but requested data on the effect of Zocor on lipid parameters.

The Scandinavian Simvastatin Survival Study (4S) was the longest and largest placebo controlled trial of simvastatin involving treatment of 4444 patients (2221 on simvastatin) for a median of 5.4 years. The data was reported as a non promotional, factual summary of the aims, design and results of the study. It included the effects on lipid parameters and data on clinical endpoints. This was highly relevant to assessing the efficacy of the treatment. One of the primary aims of reducing raised cholesterol was to reduce the risk of coronary events and mortality from CHD. It was perfectly reasonable that a letter responding to a request for information comparing the efficacy of simvastatin and any other statin should include a summary of the most up to date representative data from the longest and largest study of simvastatin in the treatment of hypercholesterolaemia.

The summary of Scandinavian Simvastatin Survival Study appeared under the headline "Effect on CHD", not specifically within the section on atorvastatin. The inclusion of the summary of the Scandinavian Simvastatin Survival Study was highly relevant to the enquiry and was not promotional so that this letter was outside Clause 1.2 of the Code. The data presented was not misleading or disparaging to atorvastatin so would not be in breach of Clauses 7.2 or 8.2 of the Code.

2 Complaint: Bold type was used for the statement "... There are no published studies in which the effect of atorvastatin on the clinical outcomes of coronary heart disease (CHD) has been studied."

Merck Sharp & Dohme pointed out that this statement was true at the time the letter was sent and still was true.

One of the primary aims of treating hypercholesterolaemia was to reduce the risk of coronary events and mortality from CHD. The Scandinavian Simvastatin Survival Study demonstrated that simvastatin reduced both coronary and total mortality in post myocardial infarction and angina patients with raised cholesterol. At the time this letter was sent there was no data showing that atorvastatin had any beneficial effect on long term outcomes of reduction in morbidity and mortality from CHD. There were no comparative studies showing the differences between atorvastatin and simvastatin on long term outcomes. If such data became available it would of course be included.

The bold type was used simply to differentiate the atorvastatin data from the simvastatin data but in view of the concerns of Parke Davis this had been changed so that bold type was no longer used.

The reference to endpoint data was highly relevant to the prescriber, pharmacist and the patient. This statement was accurate and not misleading. It was not promotional so that this letter remained outside Clause 1.2 of the Code. This statement was accurate and not misleading and not disparaging to atorvastatin so would not be in breach of Clauses 7.2 and 8.1 of the Code.

3 Complaint: Summary section

This letter was sent in response to an individual enquiry by a pharmacist and contained only relevant information so it was outside Clause 1.2 of the Code. The brief factual summary highlighted the major differences between the two medicines at the time of writing.

One of the major differences was that simvastatin was licensed for reduction of specific endpoints (reduction of mortality and morbidity from CHD) and not just to show biochemical improvements. Atorvastatin was not licensed for reduction of clinical endpoints and as there were no studies showing any long term benefit of atorvastatin on coronary morbidity or mortality a class effect could not be assumed. This was of enormous clinical importance.

The second point was the difference between the amount of clinical data available for simvastatin which had been available for over eight years and the relatively little data for atorvastatin which had been available for just a few months. In order not to mislead the reader the final sentence explained the differences in patient experience by stating "... as would be expected for any product soon after launch ...". The current atorvastatin product monograph stated "administered to over 2,500 patients in over twenty studies amounting to 1845 patient-years of exposure". There was far greater patient experience in the Scandinavian Simvastatin Survival Study alone and, overall, 6,700,000 patients had been treated with simvastatin. The letter could even have stated that there was a more than 2000-fold difference in experience!

The style used in this particular letter spaced the sentences. There were no 'bullets' to suggest that these were 'stabpoints'; this was merely a question of style. Merck Sharp & Dohme did not believe that the style of these sentences amounted to promotion.

The name Zocor appeared throughout the letter in capital letters as it was a registered trade mark. Indeed, it was common practice throughout the pharmaceutical and other industries to differentiate registered trade marks by

the use of capital letters. The use of the brand name was a point of style and did not in itself amount to promotion. However, in an attempt to resolve this matter amicably, Zocor no longer appeared in capital letters in the current letter.

This summary was, therefore, not promotional and under Clause 1.2 of the Code. The statements were factual, capable of substantiation and, whilst Merck Sharp & Dohme denied that any of the stylistic matters raised by the complainant amounted in any way to promotion, these had already been modified in an attempt to meet its concerns.

4 Complaint: "No prescribing information or direction to prescribing information: no date of preparation or revision".

The letter was non promotional and sent in response to a specific enquiry from a pharmacist on comparative efficacy of the statins and effects of Zocor on lipid parameters. It was, therefore, outside Clause 1.2 of the Code.

The letter contained relevant information on the licensed indications, described the comparative studies of atorvastatin and simvastatin, and included a non comparative section on the known effects of the two medicines on CHD, the results in diabetics, effects on trigylcerides and long term tolerability data. There was no requirement for prescribing information to be included with an individual response to an enquiry.

The date of preparation and revision of an individual letter was the date shown at the top of each letter.

This letter contained only information that was highly relevant to the enquiry and it, therefore, could not be deemed promotional so prescribing information was not required and was outside the Code.

5 Complaint: Comparisons between simvastatin and atorvastatin - reference to potency

Parke Davis had complained about the use of the following statements:

"When drawing conclusions from the following studies it should be borne in mind that the relative potency has not been confirmed in large scale clinical trials; therefore the studies may not look at comparable dosages."

"These results are not unexpected as the doses used were not equipotent."

"By analysis of covariance the effects on total cholesterol and LDL cholesterol were significantly greater for atorvastatin, which would not be unexpected as non-equipotent doses were compared."

"Further head to head studies using equipotent doses are clearly needed to compare the long term efficacy and safety of atorvastatin with simvastatin."

Merck Sharp & Dohme said that the letter had been sent in response to a specific enquiry from a pharmacist on comparative efficacy of the statins and was, therefore, non promotional under Clause 1.2 of the Code. The results from the studies were presented in a fair and balanced way so as not to mislead, and the letter made no statements claiming superior potency for simvastatin in relation to weight. Therefore, Merck Sharp & Dohme did not believe it was in breach of Clause 7.2 of the Code.

The letter responsibly pointed out that the relative potency of simvastatin and atorvastatin had not been clearly defined at the time the letter was written. The statements in the letter were in full agreement with the conclusion from the only head to head comparison of atorvastatin and simvastatin published as a full paper at the time the letter was sent. The authors had stated "Longer term studies in a larger cohort of NIDDM [non insulin dependent diabetes mellitus] patients will establish more definitely the relative potencies of simvastatin and atorvastatin". That study (Best) presented open label data on 25 patients with non insulin dependent diabetes treated for just four weeks. As it was a small, short term, open label study, the results obviously required confirmation in larger studies.

At the time of writing the letter, there were just three head to head comparisons of atorvastatin and simvastatin - only one of these had been published in full and the other two were preliminary results.

Data from small unpublished open label studies must always be viewed with caution and it was not misleading or disparaging to alert the enquirer to the limitations of such data. As new data comparing atorvastatin with simvastatin had appeared for atorvastatin, this section had been continually updated to include this and there were no longer any references to the issue of potency.

There was no suggestion in the letter sent out by Merck Sharp & Dohme's medical information department that the studies were of questionable relevance, but the limitations of such small open label preliminary results had to be recognised. The presentation of the data available was not disparaging to atorvastatin as it presented all the available data comparing simvastatin and atorvastatin in a clear concise way and so not in breach of Clauses 8.1 or 8.2.

The letter was sent in response to an enquiry from a health care professional and presented relevant, and up to date, data comparing atorvastatin and simvastatin in a fair and balanced way. It was not promotional in nature and, therefore, was excluded from the terms of the Code under Clause 1.2. As a non-promotional item it did not require prescribing information and so was not in breach of Clause 4.1, 4.6 or 4.7. The information in the letter was not misleading and contained no claims for superior potency in relation to weight and so was not in breach of Clause 7.2 of the Code. It was not disparaging to atorvastatin or disparaging to clinical and scientific opinions of other health professionals and so was not in breach of Clauses 8.1 and 8.2.

This letter was sent as an individual response to a specific enquiry and was based on the most up to date information at the time. The paragraphs on which it was based had been changed substantially as they were frequently updated as new data became available.

PANEL RULING

The Panel noted that as the medical information letter had been sent in 1997 the requirements of the 1996 Code applied. Clause 1.2 of the 1996 Code stated that the term

promotion did not include "replies made in response to individual enquiries from members of the health professions or in response to specific communications whether of enquiry or comment, including letters published in professionals journals, but only if they relate solely to the subject matter of the letter or enquiry and are not promotional in nature.". (The 1998 Code had been changed so that, although the same exemption applied, the final part of it read "... but only if they relate solely to the subject matter of the letter or enquiry, *are accurate and do not mislead* and are not promotional in nature.". The purpose of the amendment was to give details about how the clause was interpreted.)

The Panel had first to decide whether or not the letter was subject to the Code. The Panel noted that the pharmacist had asked Merck Sharp & Dohme for data comparing its product with other statins and also non-comparative data demonstrating Zocor's effect on various blood lipid levels. The Panel noted that the letter compared Zocor with four other statins and also provided details of the 4S study which evaluated the effect of Zocor in patients with established CHD. The Panel considered that the letter responded to the two points raised by the enquirer and in terms of its content the letter related solely to the subject of the enquiry.

The Panel made a number of comments about the letter's style and presentation. It noted that although for the most part the generic name of Zocor, simvastatin, had been used, each mention of Zocor as the brand name was in capitals. The Panel noted that the summary to the section comparing Zocor and atorvastatin had not been written in the usual narrative style of a letter. The Panel considered that most readers would view the summary as a series of bullet points such as were more usually associated with advertising. The Panel noted that three of the four points were statements about Zocor, giving its indications, details about the number of patients who had used the product and stating that there was a wealth of published information concerning the long term efficacy and safety of Zocor. The brand name Zocor appeared in capitals. The last point stated that atorvastatin was one of the newest HMG-CoA reductase inhibitors for which, as expected for any product soon after launch, there was limited available published comparative data. The Panel noted that a section detailing the effect of Zocor in CHD was headed, in bold, with the sentence "There are no published studies in which the effect of atorvastatin on the clinical outcomes of coronary heart disease (CHD) has been studied, either in primary or secondary prevention". The Panel noted that atorvastatin was not licensed for use in CHD (ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998-99). Overall the Panel considered that, in terms of style, the letter went beyond the exemption provided in Clause 1.2 of the Code. It was not an unbiased discussion of the effect of Zocor alone or in comparison with other statins. The brand name Zocor always appeared in capitals and positive statements for Zocor and those critical of atorvastatin had been presented in a prominent manner. The Panel considered, therefore, that the letter was promotional in nature and therefore subject to the Code.

The Panel noted that the section of the letter headed "Zocor: Comparison with atorvastatin" contained a number of sub-sections, three of which discussed the 4S study. The 4S study was a placebo-controlled evaluation of Zocor in patients with established CHD. The Panel considered that contrary to Merck Sharp & Dohme's submission, the 4S data was specifically included in the atorvastatin section as it came within the main section entitled "Zocor: Comparison with atorvastatin" and in between other sections which discussed both Zocor and atorvastatin. The Panel considered that although it was appropriate to include details about the 4S study it was not appropriate to include the details in the middle of a section headed "Zocor: Comparison with atorvastatin". The first of the three sub-sections concerned with the 4S study was headed "Effect on CHD" followed by a statement, in bold, that there were no published studies in which the effect of atorvastatin on the clinical outcomes of CHD had been studied, either in primary or secondary prevention. The Panel noted that atorvastatin was not licensed for use in patients with CHD. The Panel considered that it was misleading to include the 4S data in a section comparing Zocor with atorvastatin. A breach of Clause 7.2 was ruled. In addition the Panel considered that the statement regarding the lack of published studies on atorvastatin and CHD, although true, was misleading given that the product was not licensed for use in CHD. A further breach of Clause 7.2 of the Code was ruled.

The Panel noted that as a consequence of the letter being considered to be subject to the Code, it should have included prescribing information for Zocor and, as it was more than four pages long, the letter should have included a reference as to where the prescribing information could be found. As both pieces of information were missing the Panel ruled breaches of Clauses 4.1 and 4.6 of the Code. The Panel considered that the date on which the letter was sent constituted the date on which the letter was prepared and ruled no breach of Clause 4.7.

The Panel noted that the letter presented data from a number of studies which had compared the efficacy of Zocor with atorvastatin in the treatment of hypercholesterolaemia. The introduction to this section of the letter included the sentence "When drawing conclusions from the following studies it should be borne in mind that the relative potency has not been confirmed in large scale trials: therefore, these studies may not look at comparable dosages". In addition, the description of two trials cast doubt upon the validity of the positive results for atorvastatin by stating that the doses of atorvastatin and Zocor which had been compared had not been equipotent. The Panel noted, however, that in almost all cases the doses of the two products had been those licensed for the treatment of hypercholesterolaemia. (In one trial atorvastatin had been given in doses of either 5mg or 20mg whereas the lowest licensed dose was 10mg). The Panel considered that the statements disparaged atorvastatin and ruled a breach of Clause 8.1 of the Code. The Panel did not consider, however, that the statements amounted to disparagement of the clinical and scientific opinions of the various authors as alleged. No breach of Clause 8.2 was ruled.

Complaint received **16 December 1997**

Case completed **27 May 1998**

CASE AUTH/662/1/98

CONSULTANT HAEMATOLOGIST v WYETH

Zoton advertisement

A consultant haematologist complained about an advertisement for Zoton issued by Wyeth. The advertisement featured a man posing in an artist's studio with a caption which read "Professor —. Portrait painter. No ordinary surgeon". In small print beneath it was stated that "The appearance of Professor — in this advertisement does not imply that he endorses the product advertised". The complainant drew attention to the requirement of the Code that "The name or photograph of a member of a health profession must not be used in any way that is contrary to the conventions of that profession.". The complainant considered that the advertisement was designed to create the impression that the professor endorsed the product and it was thus irresponsible and unethical. In the complainant's view, the professor's involvement in the advertisement was contrary to the conventions of his profession.

In the Panel's view, the requirement of the Code mentioned by the complainant referred to the fact that health professionals were not supposed to endorse products. It was not customary practice for health professionals to appear in advertisements. In the advertisement in question the Panel considered that the professor would inevitably be seen as endorsing Zoton. The Panel did not consider that the inclusion of a disclaimer would remove this impression. A breach of the Code was ruled.

Upon appeal by Wyeth, the Appeal Board noted that the professor was a transplant surgeon and unlikely to have professional involvement in the area of medicine for which Zoton was indicated. In the Appeal Board's view, however, the majority of readers would assume that his appearance was nonetheless an endorsement. It was a principle of the Code that misleading impressions could not be corrected by footnotes or disclaimers. The Appeal Board noted that the professor was pre-eminent in his profession and considered that his reputation would be seen as adding prestige to his implied endorsement of Zoton. The Appeal Board upheld the Panel's ruling that there had been a breach of the Code.

A consultant haematologist complained about a Zoton advertisement (ZOT689/0697) issued by Wyeth Laboratories.

COMPLAINT

The advertisement contained a photograph of a man posing in an artist's studio and a caption which read "Professor —. Portrait painter. No ordinary surgeon.". The complainant stated that embedded in the text below, in print so small as to be barely readable, was the following sentence: "The appearance of Professor — in this advertisement does not imply that he endorses the product advertised.". The complainant understood that the advertisement was one of a set of four featuring eminent doctors. The complainant drew attention to Clause 9.2 of the Code which stated "The name or photograph of a member of a health profession must not be used in any way that is contrary to the conventions of that profession." and that companies must abide by both the letter and the spirit of the Code.

The complainant said that the basis of his complaint was:

1 The advertisement was designed to create the impression that the professor endorsed the product. It was thus irresponsible and unethical.

The complainant stated that Wyeth was aware that many people who saw the advertisement would not read the disclaimer and that those who did would already have formed a potentially durable mental link between Zoton and the professor. The advertisement was a cynical attempt to circumvent the strict controls that existed on the endorsement of medicines by medical practitioners. Irrespective of whether the Panel considered the advertisement complied with the Code in the letter, it must surely accept that it breached it in the spirit.

2 Professor — 's involvement in the advertisement was contrary to the conventions of his profession.

The complainant stated that professionals must act - and be perceived to act - in a professional way. The professor should have realised that, rightly or wrongly, many readers would assume that his appearance represented an implicit endorsement and that it was motivated by financial gain. Whether he actually benefited financially was irrelevant: it was how his behaviour was likely to be perceived that mattered.

The complainant added that if the Panel did not believe that people would perceive the professor's behaviour in this way, how did it think they would perceive it?

3 For the Panel to conclude that the advertisement complied with the Code would set an appalling precedent and open the gates to massive abuse of a similar kind in the future.

The complainant asked where would such 'endorsement by the back door' stop?

The complainant was aware that the professor willingly consented to his photograph being used. The complainant was also aware that the Authority expressed profound misgivings about the advertisement at concept stage, and that Wyeth had pressed ahead regardless.

The complainant urged the Panel to ban the advertisement.

RESPONSE

Wyeth submitted that the theme for the campaign was "Out of the Ordinary" and this was supported by the use of images of four medical practitioners who had unusual extra-professional hobbies or pastimes. So, in addition to the professor, the company had used images of doctors who were respectively a polar explorer, a water skiing champion and an Anglican priest. The company

commented that the complainant was quite incorrect when he referred to the use of "eminent doctors". The focus was not the doctors' professional reputation (eminent though the professor undoubtedly was) but what they had achieved outside the field of medicine.

Wyeth stated that when this campaign was in the planning stage, it was very much aware of the provisions of Clause 9.2 of the Code. Although this clause did not of course absolutely prohibit the use of the name or photograph of a health professional, the company recognised the need to ensure that nothing it was asking the participating doctors to do was contrary to the conventions of the medical profession. This was reinforced by the Authority with whom the general principles were discussed at this stage although Wyeth emphasised that "profound misgivings" were not expressed as the complainant had suggested.

Wyeth said that the light of its own assessment and of the advice received, it took the following preparatory steps.

1 Wyeth's Legal Department wrote to the General Medical Council and was advised that any doctor considering participating in the campaign should obtain the advice of his or her medical defence organisation before agreeing to take part.

2 All the doctors who participated, including the professor, were advised in writing by Wyeth of the GMC's advice.

3 Wyeth required and received from all participating doctors written confirmation that they had either contacted their defence organisations or had made a decision not to do so.

4 In all but one case, the doctors consulted their defence organisations and where those organisations requested special conditions (eg the form of wording for the disclaimer) these were incorporated into the advertisements.

5 All the participating doctors saw and approved the final advertisements before they were released to the press for publication.

Wyeth submitted that it went to some lengths to ensure that the participating doctors were not placed in a position where their professional status was compromised and it followed that there had been no breach of Clause 9.2, or indeed of any other provision of the Code. The company did not accept that there had been "endorsement by the back door" as the complainant had alleged.

PANEL RULING

The Authority had given Wyeth informal advice about the "out of the ordinary" advertisement concept in relation to the requirements of Clause 9.2 of the Code. The Authority had not seen the advertisement but had expressed misgivings. The Authority could only give informal advice and if a complaint was subsequently received it would be dealt with in the usual way.

The Panel noted that the colour photograph of the professor was the main focus of the advertisement. Beneath the picture a caption read: "Professor —. Portrait painter. No ordinary surgeon". There followed a number of claims for Zoton and then, in small print, the disclaimer "The appearance of Professor — in this advertisement does not imply that he endorses the product advertised". At the bottom of the advertisement Zoton was printed in prominent logo type, accompanied by the statement "In maintenance therapy It's out of the ordinary".

The Panel noted that Clause 9.2 of the Code stated that "The name or photograph of a member of a health profession must not be used in any way that is contrary to the conventions of that profession". In the Panel's view Clause 9.2 referred to the fact that health professionals were not supposed to endorse products. The Panel noted that it was not customary practice for members of the health professions to appear in advertisements. In the advertisement in question the Panel considered that the professor would inevitably be seen as endorsing Zoton. The Panel did not consider that the inclusion of a disclaimer would remove this impression. A breach of Clause 9.2 was ruled.

APPEAL BY WYETH

Wyeth noted that Clause 9.2 stated that a doctor's name and photograph should not be used in any way that was contrary to the conventions of the medical profession. In concluding that the advertisement in question did breach this clause, the Panel was of the opinion that the appearance of the professor amounted to an endorsement of the product which in turn necessarily amounted to a breach of the medical profession's conventions.

Wyeth again took issue on the implied endorsement point. It was not only Wyeth's view that there had been no endorsement in the present case; this also appeared to be the view of the medical profession at large. Why else would widespread publication over a period of 9 months, involving a total of 3.8 million opportunities to view the advertisement (number of journal insertions x readership), produce just this one complaint. In Wyeth's view, it was plain that the profession did not see the professor's participation as promotional and Wyeth submitted that the Panel should not have substituted its own views on these matters for those of the profession itself. Accordingly, it was Wyeth's case that the advertisement was not contrary to the conventions of the medical profession and that no breach of Clause 9.2 had occurred.

Wyeth also pointed out that if the Panel's ruling were to be upheld, this would call into question a number of other established practices, such as the appearance of doctors in product videos and symposia reports, which, on the basis of the test applied by the Panel, would also be deemed to amount to endorsement.

The company again stated that the General Medical Council had advised the company that endorsement might be an issue and advised that participating doctors should seek the views of their medical defence organisations.

APPEAL BOARD RULING

The Appeal Board noted that the professor was a transplant surgeon and unlikely to have professional involvement in the area of medicine for which Zoton was indicated. In the Appeal Board's view, however, the

majority of readers would assume that his appearance in the advertisement was nonetheless an endorsement of the product. The Appeal Board did not consider that the disclaimer removed this impression. The Appeal Board noted that it was a principle under the Code that misleading impressions could not be corrected by footnotes or disclaimers etc. It was not customary practice for photographs of health professionals to be used in advertising. The Appeal Board noted that the professor was pre-eminent in his profession and considered that his reputation would be seen as adding prestige to his implied endorsement of Zoton. The Appeal Board upheld the Panel's ruling of a breach of Clause 9.2 of the Code.

The appeal therefore failed.

The Appeal Board considered that there was a distinction between the advertisement now before it and the appearance of doctors in company sponsored videos, symposia reports and the like. In the latter, doctors passed on clinical expertise or scientific knowledge rather than solely product endorsement.

Complaint received **5 January 1998**

Case completed **27 May 1998**

CASE AUTH/663/1/98

NO BREACH OF THE CODE

HOSPITAL RESEARCH ETHICS COMMITTEE v ZENECA PHARMA

Zomig study

A hospital research ethics committee complained about a study on Zomig (zolmitriptan) in the treatment of acute migraine which was to be undertaken on behalf of Zeneca Pharma. The aim was to compare the time to onset of perceived action by assessing the time to first detectable migraine relief of two doses, 2.5mg and 5mg. The complainant said that previous studies looked at headache response in hours. This study intended to look at the response during the initial two hours at 15 minute intervals, 30 minute intervals etc. In the complainant's view, it was unlikely that there would be any relief before one hour and any difference between 2.5mg and 5mg. In the documentation it was specifically mentioned that decreases in migraine symptoms were evident within one hour and that improvement continued for up to four hours. The complainant's view was that in a way the trial had already been done in migraine clinics but using the start point at one hour. In view of this, the complainant alleged that the intention to recruit 150 general practitioners was a form of promotion. The ethics committee felt strongly that the trial was an attempt to persuade general practitioners to use zolmitriptan instead of sumatriptan.

The Panel noted that the only requirement in the Code relating to clinical trials and the like was that such trials must not be disguised promotion. Any study would inevitably have some promotional impact but studies must not be promotional *per se*. They must be designed to address a valid clinical objective. The Panel noted that although the two doses had been compared in previous studies, the proposed study differed in several respects. Patients were required to take the treatment when, in the patient's opinion, the migraine headache warranted taking the medication. It was acceptable to treat any severity of headache, mild, moderate or severe. In previous studies assessment was undertaken when headache was moderate or severe. The patient assessment of time to first detectable migraine relief and time to meaningful migraine relief might comprise a different group of symptoms for each patient and would not necessarily be the same assessment of headache as had been carried out in previous studies. Relief of symptoms was likely to differ from the patient assessments of headache in previous studies and assessments would be made at different time intervals to most of the previous studies. The Panel considered that overall the study was not promotional in nature and ruled no breach of the Code.

A hospital research ethics committee complained about a study on Zomig (zolmitriptan) in the treatment of acute migraine which was to be undertaken on behalf of Zeneca Pharma. The aim of the randomised double-blind parallel group multicentre study was to compare the time to onset of perceived action of Zomig by assessing the time to first detectable migraine relief of two doses, 2.5mg and 5mg. The study protocol had been submitted to the ethics committee by a general practitioner for ethical review.

COMPLAINT

The complainant stated that the study required the general practitioner to assess the time taken to detect migraine relief and considered that since Zomig was already on general release this could easily be done in any clinic. Furthermore, given the large number of centres involved in the study, the complainant considered that, at face value, it could be a marketing exercise. Reference was made to Clause 10 of the Code.

The application specifically mentioned that 150 general practice centres were involved, providing 8 patients each.

The complainant stated that in the protocol there was a direct comparison of dosage and efficacy. The dosage used was 1mg, 2.5mg, 5mg and 10mg. The study was to compare 2.5mg with 5mg. The previous studies looked at the headache response in hours. This study intended to look at the response during the initial 2 hours at 15 minute intervals, 30 minute intervals etc.

The complainant stated that it was very unlikely that there would be any relief before 1 hour and any difference between 2.5mg and 5mg. The documents provided by Zeneca mentioned that decreases in migraine symptoms were evident within 1 hour of administration of the first tablet and improvement continued up to 4 hours. The complainant's view was that in a way the trial had already been done in migraine clinics but using the start point at 1 hour. The table in the protocol showed there was no real difference in the headache response at 2.5mg and 5mg.

In the light of this evidence, the complainant alleged that the intention to recruit 150 general practitioners was a form of promotion. There were many migraine clinics in the country which dealt with patients presenting with acute migraine, during the attack, and soon after the onset. The change in venue from migraine clinics to general practice was not suitable and was unlikely to lead to any useful information.

The complainant stated that the ethics committee felt strongly that this trial was an attempt at promotional acceptance by general practitioners to use zolmitriptan instead of sumatriptan.

RESPONSE

Zeneca did not accept that this study was in breach of Clause 10.2 of the Code and submitted that its response would confirm that the study was clinically justifiable and designed to answer valid and important therapeutic questions.

Study rationale

Zeneca stated that despite recent advances in research and the expansion of available treatments, epidemiological studies had shown that migraine was the most common neurological disorder, affecting approximately 10% of adults, and often remained under-diagnosed and inadequately treated. The effect of this on the individual

sufferer was that the pain could be intense, prolonged and unpredictable, and often resulted in withdrawal from normal activities thus affecting work, social and family life.

In a recent survey of 500 self-diagnosed sufferers of migraine, the most important features of migraine medication identified were: rapid relief, effective relief of headache, decrease in the likelihood of recurrence, treatment that did not cause nausea

Zeneca stated that as speed of relief/onset of action were important facets of the management of migraine, the study comparing two doses of zolmitriptan, both of which were in accordance with the UK marketing authorization, had been designed to confirm earlier, preliminary findings that patients might also achieve benefit within one hour of starting treatment, particularly with the higher, 5mg dose. Most of the available efficacy data for zolmitriptan had been established from placebo controlled trials and had shown that in terms of relief of headache at two hours, the primary efficacy measure "headache response", there was a response in 63% of patients treated with 2.5mg and 5mg of zolmitriptan. However, these patients did not treat their headache until the pain intensity became moderate or severe ie they did not treat mild pain.

Patients recruited into the study were able to treat their migraine when they felt it required treating, irrespective of grade of severity. Thus, the data collected would provide not only new data on the relief of headache pain, regardless of severity, but relief of associated symptoms and impact on daily life.

Zeneca stated that to assess the specific requirements of rapid onset of action in this study, the time at which patients first experienced detectable symptom relief and when relief became meaningful to them were recorded. The efficacy and safety assessments were also made at 15, 30, 45, 60, 90 and 120 minutes after the start of treatment thus providing more detailed data than was presently available. In addition, valuable prescribing information would be collected which would help clarify the additional benefit, if any, of the higher dose (5mg), currently recommended for subsequent attacks where the initial 2.5mg was not fully effective. The study design was, therefore, significantly different from previous trials and set out to provide answers to important clinical questions, contrary to the complainant's suggestion that this had already been done in migraine clinics.

Recruitment

Zeneca stated that the study was a naturalistic study being conducted on an international multicentre basis and had been set up in accordance with the principles of Good Clinical Practice (as laid out in the International Conference on Harmonisation document) "Good Clinical Practice: Consolidated Guideline" and the Declaration of Helsinki. Fifteen countries, including the UK, were participating and 150 centres worldwide were to be set up. To date, there were 137 study centres and of these, 52 centres were based in the UK with approval from 46 ethics committees. In the UK, it was mainly GPs who treated migraine patients and thus the trial reflected clinical practice in the UK. Patient recruitment was currently 805 patients; 333 of whom were based in the UK.

Sample size

Zeneca stated that the sample size for the study was calculated in accordance with recognised statistical methods to give sufficient power to detect the anticipated difference and hence fulfil the scientific objective of the study.

It was expected that the majority of the patients would treat their migraine when the headache pain was mild. As there was insufficient data on treating migraine in patients with mild headache pain, the sample size was based on a previous zolmitriptan study where patients treated their migraine headache when it was moderate or severe. It was also expected that patients treating migraine when the headache was mild would have a better response and hence the estimated sample size was an overestimate.

From a previous study, 53% of patients treating a migraine with 2.5mg experienced meaningful migraine relief two hours after dosing. For a 5mg dose, a 10% improvement at two hours after dosing was regarded as being of sufficient clinical importance to justify the use of the higher dose. For meaningful migraine relief, 970 patients (485 per group) were needed in order to detect a 10% improvement from the 2.5mg dose in the percentage of patients experiencing meaningful migraine relief, at two hours after dosing, with 90% power with 5% significance level. Zeneca submitted that since the time to first detection of migraine relief would occur before time to meaningful migraine relief, 970 patients would be sufficient to detect a difference between 2.5mg and 5mg, two hours after dosing, of 10% with at least 90% power and 5% significance level.

Zeneca stated that in order to allow a 15% drop out rate, 1,142 patients would be required and, therefore, the study aimed to recruit approximately 1,200 patients. In order to achieve this, each participating centre would aim to recruit a minimum of 8 randomised patients (8-10 patients/centre was normal for migraine studies). This target of 8 plus randomised patients could be difficult to achieve in that approximately 40% of migraine sufferers in the UK did not consult a physician and that, on average, only 2 patients per month per investigator would be suitable for recruitment. After diagnosis migraine sufferers would frequently self treat with over-the-counter medications and did not use prescription medicines.

Investigator remuneration

Zeneca stated that payment to UK investigators was £400 per patient per completed case record form. This flat payment was to cover all the GP's time and any ancillary investigative costs, including two assessment visits, ethical committee approval, patient travel and, where relevant, any pharmacy costs. Although the actual time spent would vary for each investigator and individual patients, it was estimated that participation in the study would involve approximately 3 hours. Therefore, investigator remuneration for the study was in accordance with that specified in the British Medical Association's guidelines of £116 - £150 per hour.

Conclusion

Zeneca submitted that the study had valid scientific

objectives and had been designed accordingly to answer these objectives. Zeneca considered both the sample size, number and international coverage of study centres to be appropriate and, therefore, not disguised promotion.

PANEL RULING

The Panel noted that the only requirement in the Code relating to clinical trials and the like was Clause 10.2 of the Code which required that such trials must not be disguised promotion. The Panel accepted that any study would inevitably have some promotional impact, but studies must not be such that they were promotional *per se*. Studies must be designed to address a valid clinical objective.

The Panel noted that the study was to be conducted in 150 centres worldwide, each centre recruiting 8-10 patients. In the UK the study was to be conducted in general practice centres. This reflected clinical practice in the UK where most patients were treated in general practice and migraine clinics were secondary referral centres.

The study protocol stated that it was an international, multi-centre, randomised, double-blind parallel group trial in 1200 patients with an established diagnosis of migraine. The study consisted of two visits: the initial screening visit at which patients would receive one treatment pack of zolmitriptan or placebo and thereafter had a maximum of 12 weeks in which to treat an attack and return for follow up assessment. The patient would complete a migraine headache diary.

The Panel noted that the study's primary objective was to compare the time to onset of action of a 2.5mg and 5mg oral dose of zolmitriptan by recording the time at which patients experienced the first detectable relief from their migraine and when this relief became meaningful to them. The secondary objective was to assess other efficacy measures and the safety of the two doses of zolmitriptan. Response to treatment would be assessed at 15, 30, 45, 60, 90 and 120 minutes after the first dose by recording intensity of headache pain and associated symptoms, impact on normal activities, use of a second dose of investigational product and/or other escape medication. The incidence and nature of adverse events would also be recorded.

The Panel noted that although the two doses had been compared in previous studies, the proposed study differed from these in several aspects. Patients were required to take the treatment when, in the patient's opinion, the migraine headache warranted taking the medication. It was acceptable to treat any severity of headache, mild, moderate or severe. In previous studies assessment was undertaken when headache was moderate or severe. The patient assessment of time to first detectable migraine relief and time to meaningful migraine relief might comprise a different group of symptoms for each patient and would not necessarily be the same assessment of headache as had been carried out in previous studies. Relief of symptoms was likely to differ from the patient assessments of headache in previous studies and assessments were made at different time intervals to most of the previous studies.

The Panel considered that the payment of £400 per patient per completed case form was on the limits of acceptability given that the British Medical Association suggested fee for participation in clinical trials was, according to the Authority's information, £126 per hour.

The Panel considered that overall the study was not promotional in nature and ruled no breach of Clause 10.2 of the Code.

Complaint received **6 January 1998**

Case completed **29 May 1998**

CASE AUTH/664/1/98

GENERAL PRACTITIONER v ASTRA

Press article on Colazide

A general practitioner complained about an article in the Daily Mail headed "Tablets that gave me back my life" which referred to Colazide (balsalazide), an Astra product. The article had been brought in by a patient with great excitement. The complainant had been unaware of the medicine previously and he was concerned about the article which seemed to claim falsely that balsalazide was "about twice as effective as other drugs". His patient's hopes and expectations had been falsely and cruelly raised. He alleged that the article was nothing short of an advertisement.

The Panel noted that articles in the press were judged on the information supplied by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. The Panel reviewed the press materials and the briefs for the speakers at a press briefing which had taken place. The Panel noted that Astra's public relations agency had contacted the Daily Mail querying four comments made in the article which the agency considered were outside the approved materials. The Panel did not accept that the press materials constituted an advertisement for a prescription only medicine to the general public and ruled no breach in that regard. One of the key product messages that were to be covered at the press briefing was that, in comparison to mesalazine, balsalazide had better tolerability. It had been accepted by Astra in another case that this was not a balanced reflection of all the evidence. The Panel considered that the material was not balanced and a breach of the Code was ruled.

A general practitioner complained about a newspaper article which appeared in the Daily Mail, 30 September 1997. The article was entitled "Tablets that gave me back my life" and featured the medical history of a patient who suffered from ulcerative colitis. The article referred to Colazide (balsalazide), a product marketed by Astra Pharmaceuticals Ltd.

COMPLAINT

The complainant stated that one of his patients had ulcerative colitis which was not proving easy to control. The patient took steroids, azathioprine, and sulphasalazine. The patient recently came across a newspaper article and produced it with great excitement at the surgery. The complainant alleged that the article was nothing short of an advertisement. As far as the complainant was aware, it was illegal to advertise prescription-only medicines to the general public. It seemed increasingly that pharmaceutical companies got round this by sending press releases extolling the wonders of their new and usually very expensive medicines. The complainant was particularly concerned at this long and large article which seemed to claim falsely that balsalazide "is about twice as effective as other drugs". When the patient brought the newspaper article to the complainant he was unaware of the medicine, no representative had seen him and no mailshot about it had been received. The complainant did have a MIMS detailing its release in October 1997 which clearly stated that it was no more effective than sulphasalazine, although the article did confirm that there were potentially less side effects with it.

The complainant considered that the ABPI should clamp down on this abuse of a loophole in the legislation. His patient's hopes and expectations were falsely and cruelly raised by the article. There were now so many magazines, mostly women's magazines, which now featured new advances but one could only assume that they, like this one, emanated from the pharmaceutical companies. The complainant would be grateful if the regulations concerning press releases to the media about new medicines could be looked at again. In this sort of case it was hard to deny the treatment to patients whose expectations were elevated but new medicines could have adverse effects as well as good effects.

The complainant had highlighted certain sections of the article, these being "a new prescription drug called Balsalazide", "The drug, Colazide, is available to the public from today. Three 2.25g capsules are taken three times daily" and "Studies have shown that Balsalazide developed by Astra Pharmaceuticals has fewer side effects, is about twice as effective as other drugs and can bring about a complete remission".

RESPONSE

Astra submitted that it had issued an invitation to consumer press journalists to attend a press briefing for the launch of Colazide on 30 September 1997. A copy of the invitation was provided. The Daily Mail journalist who was the author of the article could not attend the press briefing but she requested and was sent under embargo the consumer press pack and background information by Astra's public relations agency. A copy of these materials was provided.

Astra stated that all press materials were subject to internal scrutiny for compliance with the Code. The items were reviewed, approved and certified in accordance with Clause 14 of the Code.

In addition to the provision of the specified press materials, arrangements were made by the public relations agency for the journalist to interview a consultant gastroenterologist who was an expert in inflammatory bowel disease and had extensive experience of the use of Colazide. The journalist was informed by the public relations agency that two patient case studies were available for interview, one of whom was the patient referred to in the article but the journalist did not request details. The journalist went ahead and interviewed the consultant and through him was given access to interview the patient. No further written or verbal information was given to the journalist or the Daily Mail by either Astra or the public relations agency.

The Daily Mail article appeared on the day of the press briefing, 30 September 1997. Astra noted that the article contained inaccurate statements. The public relations

agency followed this up with the journalist. A copy of the letter from the public relations agency to the journalist was provided.

Astra had briefed the public relations agency and the consultant gastroenterologist in preparation for the press briefings and had taken care to select suitable patient case studies. A copy of the speakers' brief was provided. Astra submitted that the consultant was invited to participate in the launch activities as he was an expert in inflammatory bowel disease and had extensive experience with the use of Colazide. He had a balanced view of the therapeutic options for inflammatory bowel disease and it was considered that he would provide an expert overview to journalists. The presentation at the consumer press briefing covered the definition of ulcerative colitis, diagnosis and treatment options followed by information on balsalazide. The consumer press briefing took the form of one on one sessions with individual journalists and the three expert speakers. The Daily Mail journalist did not attend the press briefing and arrangements were made for her to interview the consultant at a separate time. The briefing provided for the press launch would have applied to any additional interviews undertaken with journalists.

Astra had contacted the consultant about his telephone interview with the journalist. The journalist was interested in understanding the background as to why balsalazide was different. The consultant explained the scientific technology of balsalazide and its delivery to the colon. There was only a brief mention of the comparative study of balsalazide and mesalazine during the interview. The consultant had stated that he certainly did not make a comment about other treatments being woefully inadequate, a phrase used in the Daily Mail article, since that was not his view. He considered that he expressed balanced views in the interview which was entirely what Astra would have expected.

Astra pointed out that there was no statement in the press materials which suggested that balsalazide was twice as effective as other drugs or that "Up to now treatments were woefully inadequate" as stated in the article. Furthermore there did not appear to be a basis for these statements in the interview with the consultant. Astra surmised that the statements were based on the journalist's interpretation of the information provided to her. It appeared that the journalist had misinterpreted some of the information provided in the press materials and that some of the statements in the article reflected her style of writing. The company submitted that the press materials were factual, balanced and complied with Clauses 20.1 and 20.2 of the Code. The press pack was distributed to journalists attending the consumer press briefing and also to journalists who could not attend but who requested information.

PANEL RULING

The Panel noted that complaints about articles in the press were judged on the information provided by the pharmaceutical company or its agent to the journalist and not on the content of the article itself. It was not necessarily a breach of the Code to include brand names in materials for the press.

The Panel noted that the press release consisted of two documents. The first headed "New treatment relieves the misery of ulcerative colitis" stated that ulcerative colitis patients could now be prescribed Colazide which was marketed by Astra. The document referred to a study on ulcerative colitis patients comparing balsalazide to mesalazine. The second document headed "Background information - ulcerative colitis" described the symptoms and impact of the disease, how it was diagnosed and treated. It referred to three main medical options. The document also stated that mesalazine was less likely to cause side effects than sulphasalazine. The document also referred to surgery and gave facts and figures about the disease.

The press pack also included a diagram of various parts of the gastrointestinal tract and background information on the National Association for Colitis and Crohn's Disease. The invitation to journalists to attend the press briefing was headed "New option to relieve the misery of ulcerative colitis". It stated that Colazide offered fast and effective relief for the distressing symptoms suffered by ulcerative colitis patients and referred to Colazide as an "important new treatment". The invitation stated that at the briefing a consultant physician and gastroenterologist would cover "Ulcerative colitis: What it is and how it is diagnosed and treated". A second consultant physician would deal with "From symptoms to solutions - A Typical Patient Journey", and an executive from the National Association for Colitis and Crohn's Disease would deal with "Patient needs and expectations". The invitation stated that a number of men and women with ulcerative colitis would also be available for telephone interview and that it was possible for journalists to have a one to one briefing with an expert speaker if they so wished.

The Panel noted that the speakers' brief gave details as to what the consultant physician and gastroenterologist covered in his presentation. The document referred to providing information about ulcerative colitis and then went on to give more information about balsalazide. The consultant was to cover "The key product messages" which were listed as:

"provides more rapid relief of symptoms and complete remission in more patients than mesalazine. In particular, it provides: complete remission in more patients, symptomatic remission in more patients, faster symptom relief, better tolerability, greater satisfaction with treatment"

The Panel noted the letter from the public relations agency to Astra which queried four comments made in the Daily Mail article which the public relations agency considered were outside the approved materials. The Panel noted that the public relations agency had not queried the comment that balsalazide was about "twice as effective as other drugs".

The Panel noted that 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 to the general public but the information that was made available either directly or indirectly 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 did not accept that the press materials provided by Astra constituted an advertisement for a prescription only medicine to the general public. The Panel therefore ruled no breach of Clause 20.1 of the Code.

The Panel noted that in the brief for speakers one of the key product messages that the consultant had to cover was that, in comparison to mesalazine, balsalazide had better tolerability. The Panel noted that in a previous case (Case AUTH/640/11/97) the Panel had ruled that claims that Colazide was better tolerated than mesalazine were not a balanced reflection of all the evidence and this had been accepted by Astra. The Panel considered that by including the statement regarding better tolerability compared with mesalazine, the speakers' brief was similarly not balanced. A breach of Clause 20.2 was ruled.

Complaint received 8 January 1998

Case completed 30 April 1998

CASE AUTH/665/1/98

CONSULTANT PHYSICIAN v LOREX SYNTHÉLABO

Prostate assessment clinic protocol

A consultant physician complained about a mailing sent to local general practitioners by Lorex Synthélabo which consisted of a leaflet entitled "The Prostate Assessment Clinic Protocol", a "Dear Colleagues" letter from a local consultant urologist and data sheets for two Lorex Synthélabo products, Xatral and Ditropan. It was alleged that this could be interpreted as representing a personal endorsement of those products by the consultant concerned. In the complainant's view, the company had used a colleague to endorse a particular product in a manner inconsistent with the Code.

The Panel noted that the letter from the consultant urologist made no mention of the fact that Lorex Synthélabo had sponsored the material. The company name and logo appeared only at the bottom of the final page of the protocol. The Panel considered that the sponsorship had not been made sufficiently clear. Breaches of the Code were ruled in respect of both items. The protocol referred to uroselective alpha blockers as a class and anticholinergics as a class. More than one medicine was available in each class and the Panel considered that the protocol was non promotional. The inclusion of data sheets for Lorex Synthélabo's products meant, however, that the mailing as a whole was promotional, notwithstanding the fact that they had been included at the request of the consultant urologist. The mailing was disguised promotion for Xatral and Ditropan and a breach of the Code was ruled.

A consultant physician complained about a mailing to general practitioners in his area sent out by Lorex Synthélabo Ltd. The mailing consisted of a leaflet entitled "The Prostate Assessment Clinic Protocol" accompanied by a "Dear Colleagues" letter dated 24 October 1997 written on notepaper which clearly displayed the NHS Trust logo. The letter was signed by the local consultant urologist. Data sheets for two Lorex Synthélabo products, Xatral and Ditropan, were also included. The protocol explained the procedures of the prostate assessment clinic so that it worked efficiently as a 'one-stop' clinic. The front cover of the protocol gave the names of the consultant urologist and urology nurse and a contact telephone number for the clinic. The NHS Trust logo was prominently displayed in the top right hand corner. The protocol set out the pre-referral investigations to be performed by the GP, the clinical assessments undertaken by the consultant urologist and the treatment plan. The final page, headed "Treatment Plan", stated that "The current clinical practice of the Department of Urology at ... is to use a uroselective alpha blocker as the 1st line medical management for symptomatic outflow obstruction". The Lorex Synthélabo company name and logo appeared at the bottom of this page.

COMPLAINT

The complainant stated that he had met with the consultant urologist and also corresponded with the company since he considered that this advertising could be interpreted as representing a personal endorsement by the consultant concerned of the product. The complainant's impression was that the consultant had acted very naïvely, but that the company might have breached the guidelines in respect of advertising. In the complainant's view the company had used a colleague to endorse a particular product in a manner which was outwith the Code. Furthermore, the complainant alleged that the company in correspondence to him had attempted to shift the blame to the consultant concerned, and attempted to avoid its obvious responsibility.

RESPONSE

Lorex Synthélabo stated that the production of material by hospital consultants to assist general practitioners in the diagnosis and management of various conditions was a common practice and one which was often supported by pharmaceutical companies. In the case of the condition of benign prostatic hyperplasia (BPH) in men, major developments in the diagnosis and management of this condition had occurred over the last few years, particularly the introduction of prostate assessment clinics to which GPs could refer directly without a long wait for a consultant appointment. Currently about 70% of hospitals with a urological service offered an open-access prostate clinic.

Lorex Synthélabo explained that the principle of open-access prostate assessment clinics was that after performing a basic examination and some simple tests, the GP could send the patient to the clinic for more specialised tests in order to assist with the diagnosis of

their urinary problems. The results of the tests were then sent back to the GP who would then make a management decision based on the results of the various tests. In order to make an appropriate decision it was obviously very helpful for the GP to have available management guidelines produced by the local consultant(s) suggesting the appropriate management depending on the results of the tests performed.

Lorex Synthélabo stated that this 'shared care' approach to the management of men with suspected prostate disease led to greatly improved patient management. Patients with serious disease (eg, prostate cancer) were more rapidly diagnosed, those patients that had mild to moderate symptoms of clinical BPH could be managed by their GP in accordance with the management guidelines and the number of inappropriate referrals to urologists was decreased.

Lorex Synthélabo stated that it had worked with a number of urologists across the country to provide assistance with the production of information leaflets informing GPs about the availability of local prostate assessment clinics and management guidelines to assist GPs in their management of prostate diseases.

There was no doubt that open access prostate clinics together with management guidelines enabled GPs to manage certain prostate problems, greatly enhanced patient care and Lorex Synthélabo was proud to support such initiatives.

Lorex Synthélabo turned to the specific issue of the Prostate Assessment Clinic Protocol the subject of complaint.

Lorex Synthélabo stated that the mailing consisted of a letter from a consultant urologist reminding local GPs of the existence of the prostate clinic and also reminding them of the need to refer patients to the clinic with the results of the pre-referral tests which the clinic protocol recommended. Together with the letter an assessment protocol was enclosed. This consisted of a list of recommended pre-referral investigations for the GP to perform before referring a patient, a list of the assessments that were performed in the prostate clinic and the guidelines for GPs in how to manage the patients depending on whether they had mild, moderate or severe symptoms.

As the production of the protocol was sponsored by Lorex Synthélabo, in accordance with Clause 9.9 of the Code (1996) the company name and logo was printed on it to indicate sponsorship by the company.

Lorex Synthélabo pointed out that the only recommendations as to medical treatment in the protocol referred to uroselective alpha blockers of which there were two on the market (one of which was produced by Lorex Synthélabo) and anticholinergics of which there were several on the market (one of which was produced by Lorex Synthélabo). Lorex Synthélabo pointed out that the protocol contained no references whatsoever to products produced by itself, either by brand name or generic name. The company therefore believed that the letter and the protocol between them, as they contained no specific reference to a product, should not be considered as promotional material as defined by the Code.

Lorex Synthélabo noted that the mailing as sent out, however, had also contained data sheets for Lorex Synthélabo products, Xatral and Ditropan. The company discovered that the consultant had asked Lorex Synthélabo's regional manager and local hospital representative to put these data sheets in with the protocol and covering letter prior to these being sent out. Five hundred protocols and letters were put into envelopes with data sheets for Xatral and Ditropan of which about 300 were sent out in early November via the local courier service to all the GPs in the catchment area.

Lorex Synthélabo maintained that whilst there was nothing improper in sponsoring the production of "The Prostate Assessment Clinic Protocol" and this activity would not be in breach of the Code, it recognised that by enclosing data sheets with the mailing this activity could be seen as being a disguised promotional activity in breach of Clause 10.1 of the Code. In recognition of this lapse the company had taken steps to ensure that similar instances did not occur again and had already instructed the local representative to remove the data sheets from the mailings that remained in the department.

PANEL RULING

The Panel noted that Clause 9.9 of the 1996 edition of the Code required that all material relating to medicines and their uses which was sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company. The provisions of the 1998 Code had not changed that requirement although supplementary information had been added such 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 the covering letter from the consultant urologist made no mention of the fact that Lorex Synthélabo had sponsored the material provided. This was not in accordance with Clause 9.9 of the Code. In addition the Panel noted the company name and logo only appeared at the bottom of the final page of the protocol. The Panel considered, therefore, that sponsorship of the protocol had not been made sufficiently clear to those reading it. A breach of Clause 9.9 was ruled in respect of both the letter and the protocol.

The Panel noted the exemption to the definition of promotion given in Clause 1.2 of the Code for statements relating to human health or disease provided that there was no reference, either direct or indirect, to specific medicines. The Panel considered that the protocol promoted uroselective alpha blockers as a class and anticholinergics as a class. The Panel noted that there was more than one medicine available in each class. The protocol itself did not include direct or indirect reference to a specific medicine as referred to in the exemption to the definition of promotion. The protocol itself was therefore non-promotional.

The Panel noted that the letter and the protocol had been sent out with copies of two data sheets, one for Xatral and one for Ditropan. In the Panel's view the provision of the data sheets meant that the mailing as a whole made a direct reference to specific medicines and so came within the definition of promotion in the Code. The Panel noted that Lorex Synthélabo had organised the mailing. The mailing appeared to be from an independent source informing GPs about the running of a prostate assessment clinic. The apparently independent nature of the mailing was reinforced by the prominent display of the NHS Trust

logo on both the letter and the protocol. The Panel considered, however, that due to the inclusion of the data sheets the mailing was disguised promotion for Xatral and Ditropan. The Panel ruled a breach of Clause 10.1 of the Code.

The Panel noted Lorex Synthélabo's submission that its representatives had included the data sheets in the mailing at the express request of the consultant urologist. In the opinion of the Panel, this was not relevant. The Panel noted that the company had been responsible for distributing the mailing and so it had responsibility for ensuring that it complied with the Code.

Complaint received 9 January 1998

Case completed 18 May 1998

CASES AUTH/666/1/98 AND AUTH/667/1/98 *NO BREACH OF THE CODE*

PHARMACIST v TAKEDA and ASTRA

Amias journal advertisement

A pharmacist complained about a journal advertisement for Amias which had been issued jointly by Takeda and Astra. It was alleged that the typesize used for the prescribing information was below that recommended in the supplementary information to the Code in that the height of a lower case "x" was less than 1mm in height. A further allegation concerned the wording "Am I as ... outstanding?" which appeared with an illustration showing the architectural features at the top of a skyscraper. It was alleged that the use of the word "outstanding", although posed as a question for the reader to answer, could be interpreted as meaning that the product had some special merit which set it apart from other medicines in its therapeutic class.

The Panel noted that the typesize was in fact such that a lower case "x" was 1mm in height. This was just one recommendation in the supplementary information, others referred to line length, spacing, type style, contrast and emboldening of headings. In the Panel's view the prescribing information as a whole was clear and legible and no breach was ruled.

The Panel noted that the advertisement did not make the specific claim that Amias was outstanding. Instead readers were asked to judge the issue for themselves. Beneath the quotation "Am I as ... outstanding?" the advertisement stated "You decide.". The advertisement discussed product features and concluded "The real test though, is to prescribe Amias. And then ask yourself if it stands out from the alternatives". The Panel considered that the question "Am I as ... outstanding?" was not unacceptable. It was for the reader to decide whether the features of Amias detailed in the advertisement set it apart from other treatments for hypertension. On balance the Panel considered that there had been no breach of the Code.

A pharmacist complained about an Amias (candesartan) advertisement (ref Code No AMS 2847) issued jointly by Takeda UK Limited (Case AUTH/666/1/98) and Astra Pharmaceuticals Ltd (Case AUTH/667/1/98) which had appeared in The Pharmaceutical Journal, 10 January 1998. The advertisement featured a photograph of the top portion of a skyscraper. The photograph had been taken in fading light and the architectural features at the top of the skyscraper were illuminated. Text appeared to the left hand side of the photograph and also across it to read "Am I as ... outstanding?". There were two allegations. The companies provided identical responses.

1 Print size of the prescribing information

COMPLAINT

The complainant stated that although he had no means of measuring the exact size of the typeface used for the prescribing information, the height of the lower case 'x' in the text seemed to be marginally less than the 1mm advised in the supplementary information to Clause 4.1 of the Code.

RESPONSE

Takeda and Astra submitted that the information was clear and legible and complied with the requirements of the Code. The companies noted that the complainant had stated that the height of the typeface "seemed to be marginally less" than that recommended although he did not appear to have measured it. In fact, the font used produced a lower case 'x' of exactly 1mm in height which the companies had confirmed by measuring the type size of the advertisement.

PANEL RULING

The Panel noted that Clause 4.1 of the Code stated that prescribing information must be provided in a clear and legible manner. The supplementary information to Clause 4.1 stated that legibility was not simply a question of type size and recommended a number of measures to achieve clarity. The first recommendation was that the type size should be such that a lower case 'x' was no less than 1mm in height. Other recommendations took account of line length, spacing, style of type, contrast between text and background and emboldening of headings. The Panel noted that in the advertisement a lower case 'x' in the prescribing information was exactly 1mm in height and the prescribing information had been printed in white on a black background. The supplementary information to Clause 4.1 stated that dark print on a light background was preferable. Nonetheless, in the Panel's view the prescribing information as a whole was clear and legible. No breach of Clause 4.1 was ruled.

2 Claim "Am I as ... outstanding?"

COMPLAINT

The complainant stated that the use of the word

"outstanding", although posed as a question for the reader to answer, could be interpreted as implying the product had some special merit which set it apart from other medicines in its therapeutic class. The complainant alleged a breach of Clause 7.2 of the Code.

The Authority had asked the companies to consider also the requirements of Clause 7.8 of the Code.

RESPONSE

Takeda and Astra noted that Clause 7.2 was not applicable to an allegation of implying that a product had a special merit. The text of the advertisement was based on an up-to-date evaluation of the evidence on Amias and other antihypertensives.

Takeda and Astra did not agree that the use of the word outstanding was in breach of Clause 7.8 of the Code. The companies noted that, as the complainant had correctly interpreted, the use of the word "outstanding" was in the form of a question. The words "Am I as ... outstanding?" were used in combination with the visual of a landmark, in order to ask a question of the reader. This was developed further in the text which continued "You decide" and concluded "... then ask yourself". "Outstanding" was clearly used in the context of a question; the reader decided the answer on the basis of the information provided.

Takeda and Astra submitted, however, that Amias had features which clearly differentiated the product. The dictionary definition of "outstanding" was "conspicuous, or eminent, because of excellence or remarkable in a specified field" (Oxford Encyclopaedic English Dictionary).

Angiotensin II receptor antagonists (AIIRAs) were the first new class of antihypertensives to be introduced in the past decade and were regarded as an important clinical development by cardiologists. There were now four AIIRAs available in the UK market (losartan, valsartan, irbesartan and candesartan) and there were differences between the agents in this class. Takeda and Astra submitted that Amias stood out from other antihypertensive agents for the following reasons:

- Amias was an angiotensin II receptor antagonist (AIIRA).

This class stood out from all other current classes of antihypertensive agents in that its members had a tolerability profile comparable to placebo across the dose range in clinical trials.

- Amias had been shown to demonstrate non-competitive, insurmountable binding to the AII receptor, leading to a long-sustained duration of action. This was demonstrated by its high trough:peak ratio, the highest range in the class of angiotensin II antagonists. Trough:peak ratios were recognised as being an important indicator of smooth, consistent 24-hour control of blood pressure.
- Amias demonstrated a clear dose response in efficacy with no evidence of plateauing of effect within the licensed dose range. The older members of the AIIRA class, for instance losartan, did not demonstrate a clear dose response in efficacy and demonstrated plateauing of effect at higher doses within the licensed dose range. Valsartan had been demonstrated to show similar dose for dose efficacy as losartan.
- Amias stood out from other AIIRAs in terms of price. Under the current cost constraints of the NHS it was imperative that value for money was provided by new medications. Amias was the most competitively priced AIIRA available across the recommended dose range.

PANEL RULING

The Panel noted that the complainant alleged that the use of the word "outstanding" implied a special merit for Amias. The Panel noted that Clause 7.8 of the Code stated that claims should not imply that a medicine had a special merit unless this could be substantiated. The Panel therefore considered the complaint in the context of this clause and not Clause 7.2 as referred to by the complainant.

The Panel noted that the advertisement did not make the specific claim that Amias was outstanding, instead readers were asked to judge the issue for themselves. Beneath the question "Am I as ... outstanding?", the advertisement stated "You decide." followed by "If it's a question of becoming a new landmark in the treatment of hypertension Amias has impressive qualifications. And they begin with binding". The advertisement discussed product features and concluded "The real test though, is to prescribe Amias. And then ask yourself if it stands out from the alternatives.". The Panel noted that there was no discussion of how Amias compared to other agents in the same class or with other classes of antihypertensives.

The Panel noted that Takeda and Astra stated in their responses that Amias had the highest trough:peak ratio in the class of angiotensin II antagonists although the only comparative data cited was between Amias and losartan. There was no data put forward to show how the trough:peak ratios of valsartan and irbesartan compared with that of Amias. The Panel noted the submissions that Amias was the most competitively priced AIIRA across the recommended dose range.

The Panel considered that the question in the advertisement "Am I as ... outstanding?" was not unacceptable. It was for the reader to decide whether the features of Amias detailed in the advertisement set it apart from alternative treatments for hypertension. On balance the Panel considered that there was no breach of Clause 7.8 and ruled accordingly.

Complaint received **14 January 1998**

Case completed **30 April 1998**

PHARMACEUTICAL ADVISER v ABBOTT

Agreement for loan of vaporisers

A chief pharmaceutical adviser complained about the terms of agreement for the free loan by Abbott of vaporisers for the administration of sevoflurane. The complainant considered that the purchase and subsequent use of a medicinal product should not be dependent on the use of particular equipment. The complainant had particular concerns about the wording of certain aspects of the agreement and considered that it was unreasonable to expect a hospital pharmacist to sign such an agreement.

The Panel noted that depending on personal wishes or hospital protocol there was no obligation for a pharmacy representative to sign the agreement but considered that this was not unreasonable if a hospital wished to take advantage of the loan offer. The hospital was not obliged to take up the offer. Hospitals could buy vaporisers elsewhere. The price of sevoflurane was the same whether or not the offer was taken up. The Panel considered that the arrangements should be regarded as a package deal even though the purchase of sevoflurane and the loan of vaporisers were separate transactions. The latter would not arise in the absence of the former. In the Panel's view it was not unacceptable for the vaporisers to be loaned and the arrangements were fair and reasonable. It was ruled that there had been no breach of the Code.

A chief pharmaceutical adviser complained about terms of agreement which Abbott Laboratories Limited was asking hospital pharmacists to sign.

The document in question was headed "Sevoflurane Loan Vaporisers - Terms of Agreement" and concerned the loan of vaporisers by Abbott free of charge to hospitals which purchased sevoflurane from Abbott.

Amongst the terms were:

"2. The vaporiser(s) concerned shall at all times remain the ownership (sic) of Abbott and the Hospital will have no rights in the vaporiser(s) other than as mere bailee, not withstanding the fact that any or all of the component parts in such vaporisers may be replace (sic), repaired or improved by the Hospital or any other person during the currency of this Agreement."

and

"7. Notwithstanding anything to the contrary in any Master Indemnity Agreement between Abbott and the NHS and any form of indemnity entered into pursuant thereto, the Hospital agrees to keep the vaporiser(s) in good and serviceable repair and condition, in accordance with the manufacturers recommendations, at its own cost, and shall notify Abbott of, and is responsible for making good, any damage or loss to the vaporiser(s) which may occur other than damage or loss for which Abbott is liable. Save for the above, the Hospital shall not modify or interfere with the vaporiser(s) without the written consent of Abbott."

and

"9. The Hospital shall use its best endeavours to ensure that the Vaporiser Instruction Leaflet is readily available at all times to users of the vaporiser(s) and that the vaporiser(s) are used only be (sic) fully trained and suitable personnel of the Hospital. The Hospital shall be solely responsible for and hold Abbott fully indemnified against all claims, demands, liabilities, losses, damages, proceedings, costs and expenses suffered or incurred by Abbott in any way arising out of any breach by the Hospital of this Agreement or resulting from the negligence of the Hospital, its officers, employees, agents or representatives. In the event of any incident involving the vaporiser(s) occurring, which could have a material adverse effect on Abbott's business, or the reputation of Abbott, the Hospital shall as soon as practically possible communicate the relevant facts to Abbott, and the Hospital shall seek and use its best endeavours to follow Abbott's reasonable instructions. Subject to clause 7 above and this clause 9, Abbott will indemnify the Hospital according to the terms of its Master Indemnity Agreement, reference number MIA 074.

Abbott recognises that any instructions issued to the hospital by the Medical Devices Agency in relation to any incident involving the vaporiser must take precedence over instructions issued by Abbott (where a conflict occurs)."

COMPLAINT

The complainant had a number of concerns regarding this type of marketing. Firstly, that the purchase and subsequent use of a medicinal product should not be dependent on the use of specified equipment; secondly, the complainant had particular concerns in respect of the wording of paragraphs 2 and 9; and, thirdly, the complainant considered that it was unreasonable to expect a hospital pharmacist to sign an agreement of this nature.

* * *

In writing to Abbott, the Authority drew attention to Clauses 18.1, 9.1 and 2 of the Code.

RESPONSE

Abbott stated that sevoflurane was a volatile liquid which resulted in anaesthesia following inhalation of the vaporised liquid. Administration of sevoflurane to patients required a vaporiser specifically calibrated for sevoflurane. There were several different inhalation anaesthetic agents currently available (eg isoflurane, enflurane and halothane) and each agent required a specifically calibrated vaporiser so that the concentration of anaesthetic could be accurately controlled and delivered to each patient. A volatile anaesthetic agent therefore should not be administered through a vaporiser designed for any other inhalation anaesthetic.

Abbott stated that the use of sevoflurane required a specific vaporiser designed for use with sevoflurane. However, several companies (eg Ohmeda, Blease, Penlon

and Draeger) manufactured and sold vaporisers for sevoflurane. Any hospital in the UK could purchase vaporisers from any one of these suppliers.

In Abbott's view paragraphs 2 and 9 of the agreement were perfectly normal terms for the loan of equipment to a hospital. The company was simply establishing its ownership of the device and protecting itself from claims resulting from the negligent use of its property while on loan to the hospital. The terms of agreement had been agreed with an executive at the NHS Supplies Authority.

Abbott had previously provided free-on-loan vaporisers for isoflurane and requested a signature only from a representative of the hospital anaesthetics department. The company received complaints from hospital pharmacists that they had not been involved in the arrangements. Prior to introducing sevoflurane Abbott had surveyed hospital pharmacists in England and Wales and found an overwhelming majority wished to be included in arrangements for the loan of vaporisers. For this reason Abbott included them as a signatory on the form. They were, of course, free to decline to sign if they wished or if hospital protocol prevented them from doing so.

In answer to the questions posed by the Authority when it advised Abbott of the complaint:

i) "Can a hospital buy sevoflurane at the same price whether or not it takes up the offer of vaporisers?"

Yes, Abbott's sevoflurane prices did not depend upon the loan of vaporisers.

ii) "Is the nature of sevoflurane such that vaporisers are required which differ from those which a hospital would already have for use with other anaesthetics?"

Yes as indicated above.

iii) "Did Abbott view the matter as a package deal as referred to in the supplementary information to Clause 18.1 of the Code? If so is it "fair and reasonable"?"

Abbott did not view the provision of vaporisers on free loan as a gift or as a package deal.

Vaporisers were not offered to a hospital unless a consultant anaesthetist had decided to use sevoflurane. Vaporisers were of no value to the hospital unless there was a demand from anaesthetists to use the gas.

Appropriate vaporisers were essential in order to use a gas and Abbott was prepared to offer on free loan vaporisers to facilitate the use of sevoflurane where a demand existed and the hospital was unable to provide its own vaporisers.

Abbott believed that providing vaporisers to hospitals to facilitate the use of a new gas was a much valued service to hospital anaesthetists. It allowed them to provide an anaesthetic service using their preferred anaesthetic agent, irrespective of their ability to purchase the necessary vaporiser. The placement of vaporisers was dependent upon the approval of representatives from the department of anaesthetics and the pharmacy department. Abbott considered this to be a highly ethical approach to supporting its anaesthetic product.

Abbott had referred to Clause 18.1 above but would like to clarify one further point, the supplementary information for Clause 18.1 precluded goods provided from bearing the name of any medicine. In the case of anaesthetic vaporisers it was essential that the generic name of the anaesthetic gas was shown on the vaporiser to indicate which gas the vaporiser was designed for. The International Standard ISO 5360:1993(E) for vaporisers required the name of the gas to be shown.

PANEL RULING

The Panel examined the agreement which was to be signed by three parties, an Abbott representative, a representative of the hospital and a pharmacy representative. The Panel noted, however, that depending on personal wishes or hospital protocol there was no obligation for a pharmacy representative to sign the agreement. The cost of sevoflurane was the same regardless of whether or not the hospital agreed to the terms of the loan. The hospital was not obliged to take up the offer. It was possible for the hospital to buy vaporisers elsewhere and not borrow them from Abbott. The vaporisers were of no value to the hospital unless there was a demand from anaesthetists to use sevoflurane.

The Panel noted that the supplementary information to Clause 18.1 of the Code, Package Deals, did not prevent the offer of package deals whereby the purchaser of a particular medicine received other associated benefits such as apparatus for administration providing that the transaction as a whole was fair and reasonable.

The Panel considered that the arrangements should be regarded as amounting to a package deal even though the purchase of sevoflurane and the loan of vaporisers were separate transactions. The latter would not arise in the absence of the former. In the Panel's view it was not unacceptable for the vaporisers to be loaned and the arrangements were fair and reasonable. It did not consider that it was unreasonable to expect the pharmacist to sign the agreement if a hospital wished to take advantage of the loan offer.

The Panel ruled no breach of Clause 18.1 of the Code. The Panel also ruled no breach of Clauses 2 and 9.1 of the Code.

Complaint received **16 January 1998**

Case completed **14 April 1998**

CASES AUTH/669/1/98 AND AUTH/680/2/98

PHARMACEUTICAL ADVISER and GENERAL PRACTITIONER v ABBOTT

Medical News Alert and Community Management Guidelines for Influenza in Adults

A health authority senior pharmaceutical adviser and a general practitioner complained separately about a document entitled "Medical News Alert" which was headed "Flu outbreak warning for UK doctors". It included quotations from a consultant microbiologist that "... if secondary bacterial infection is suspected, antibiotics with a wide spectrum of activity should be given ..." and that "Combination antibiotic therapy may be prescribed, however clarithromycin alone is one antibiotic which will provide effective cover against both of these infections.". Clarithromycin was an Abbott product. At the bottom of the document was the statement that it had been supplied as a medical news service by Abbott Laboratories Limited.

The pharmaceutical adviser was concerned that the news alert had been made to look like an official publication which could have been produced by the Department of Health or local health authority and alleged that it was a covert marketing exercise for clarithromycin. The complainant wondered where the quotation from the microbiologist had been obtained and whether he was aware that it was being cited in promotional material with no reference. The complainant also alleged that it was not sufficiently clear that the news alert had been produced by a pharmaceutical company despite the statement at the foot of the document. The general practitioner alleged that it was an incorrect and misleading document purporting to be a medical news service. It was no such thing. It was a thinly disguised advertisement.

The Panel considered that the document was promotional. Abbott's product clarithromycin was mentioned together with a claim for it. A breach was ruled because of the absence of prescribing information. Notwithstanding that the document had Abbott's name on it, the Panel considered that the document appeared to be an independent news alert which was not so. It constituted disguised promotional material and was ruled in breach. The microbiologist had agreed to the use of the quotation and references were only needed when published studies were referred to. No breach of the Code was ruled in those regards.

The general practitioner also complained about "Community Management Guidelines for Influenza in Adults" which he suggested had been funded by Abbott because there was subliminal advertising within it which promoted clarithromycin specifically. The sponsor had, however, not been named. The Guidelines were stated to have been issued by the Community Infections Awareness Group.

The Panel considered that the impression from the material was that the Community Infections Awareness Group was an independent group. This was not so. It had been established by Abbott but this fact had not been disclosed and a breach was ruled. The Panel considered that the Guidelines in effect promoted clarithromycin and ruled that they were in breach because of the absence of prescribing information. The Panel also ruled a breach because it considered the distribution of the Guidelines constituted disguised promotion.

Two complaints were received about a "Medical News Alert" document issued by Abbott Laboratories Limited.

The "Medical News Alert" was a one sided A4 document dated 17 December 1997. It was headed "Flu outbreak warning for UK doctors". The final paragraph included a quotation from a consultant microbiologist that "... if secondary bacterial infection is suspected, antibiotics with a wide spectrum of activity should be given ..." and that "Combination antibiotic therapy may be prescribed, however clarithromycin alone is one antibiotic which will provide effective cover against both of these infections.". Clarithromycin was one of Abbott's products. At the bottom of the document was a statement that it had been supplied as a medical news service by Abbott Laboratories Limited.

CASE AUTH/669/1/98

COMPLAINT

A health authority senior pharmaceutical adviser complained about the "Medical News Alert" which had been sent to local general practitioners. A local GP had passed it to the complainant with a comment that he had found it outrageous and unethical.

The complainant was concerned that the document had been designed to look like an official publication which could have been produced by the Department of Health or local health authority and it was in fact a covert marketing exercise for clarithromycin. This perception was enhanced by the fact that clarithromycin was mentioned by its generic and not its brand name and one would have to know that Abbott manufactured clarithromycin in order to appreciate that the document was promotional in nature.

The complainant also wondered where the quotation from the consultant microbiologist was obtained, and whether he was aware that it was being cited in promotional material (with no reference).

The complainant was uneasy about this type of promotional literature, and alleged that it did not make it sufficiently clear that it had been produced by a pharmaceutical company, despite the statement at the foot of the page.

In writing to Abbott attention was drawn to the requirements of Clauses 4.1, 9.1, 9.2 and 10.1 of the Code.

RESPONSE

Abbott explained that the "Medical News Alert" was issued by it in December 1997 and was designed to remind prescribers of the need to provide a broader spectrum of antimicrobial cover for bacterial infections

following influenza.

The "Medical News Alert" was a promotional item containing references to one of the company's products and should have included prescribing information. The company agreed that the material was in breach of Clause 4.1 of the Code and apologised for this omission. As the item was intended for single use the error should nor recur. Abbott did not accept that the "Medical News Alert" was in breach of the other clauses of the Code cited by Authority.

Abbott had a signed copy of the "Medical News Alert" from the consultant microbiologist providing evidence of his authorisation of the text including the quotation. It was obtained prior to the item being released. A copy was provided. Abbott reassured the Authority that there was no intention on the company's part that the notice should appear to be an official document issued by the Department of Health or local health authority. The name and address of the company was clearly stated on both the envelope in which the item was sent and at the bottom of the main text of the "Medical News Alert". In addition the bottom of the item contained a statement that it was being supplied as a medical news service by Abbott. The company's submission was that these provisions together with the lack of any official Department of Health insignia, should have identified the material as originating from a pharmaceutical company regardless of whether or not the reader knew clarithromycin was an Abbott product. The company submitted the material was not disguised promotion.

PANEL RULING

The Panel considered that the "Medical News Alert" was promotional. Abbott's product clarithromycin was mentioned together with a claim that it would provide effective cover against infections including *Staphylococcus aureus* and *Mycoplasma pneumoniae*. Prescribing information should have been included. The Panel therefore ruled a breach of Clause 4.1 of the Code as acknowledged by Abbott.

The Panel noted Abbott's submission that at the bottom of the document was a statement that it had been supplied as a medical news service by Abbott Laboratories Limited. Notwithstanding the fact that it had Abbott's name on it, the Panel considered that the document appeared to be an independent news alert for GPs which was not so. The Panel considered that the "Medical News Alert" constituted disguised promotional material. The Panel therefore ruled a breach of Clause 10.1 of the Code.

The Panel noted that the consultant microbiologist had agreed his quotation in the "Medical News Alert". A reference was not necessary as Clause 7.5 required references to be given only when published studies were referred to. The Panel ruled no breach of Clauses 7.5 and 9.2 of the Code in this regard.

CASE AUTH/680/2/98

This case concerned the "Medical News Alert" at issue in Case AUTH/669/1/98 referred to above. A second item "Community Management Guidelines for Influenza in Adults" was also the subject of complaint.

The "Community Management Guidelines for Influenza in Adults" was a laminated 2 sided A4 document issued by a group called the Community Infections Awareness Group. A list of the six members was given, all of whom were healthcare professionals. The Guidelines referred to patients presenting with influenza and how to proceed following examination. A flow diagram was included. Five antibiotics were listed as possible options for patients with influenza complicated by a bacterial infection who nonetheless could be treated in the community. Clarithromycin was the first antibiotic listed. The Guidelines were intended to assist GPs in determining the appropriate treatment for patients who presented with both complicated and uncomplicated flu.

COMPLAINT

A general practitioner complained about two advertisements which had been extensively circulated amongst general practitioners. The first was "Medical News Alert". The complainant alleged it was a misleading and an incorrect document purporting to be a medical news service. In fact it was no such thing, it was a thinly disguised advertisement by Abbott hoping that general practitioners would prescribe its antibiotic for people suffering from influenza.

The complainant referred to the "Community Management Guidelines for Influenza in Adults" as a more serious circular. The complainant suspected that this was funded by Abbott because there was subliminal advertising within it, which promoted clarithromycin specifically. However, the complainant could not be sure that Abbott was involved because whoever funded the Guidelines had disguised itself behind this professional group, which meant that the document had some quasi authority and would be viewed as an impartial document, which it almost certainly was not.

The complainant considered that this was a clever but dishonest advertising strategy to raise the profile of influenza, and specifically complicated bacterial infection following influenza, by Abbott, which of course manufactured a broad spectrum antibiotic. The complainant was particularly annoyed that the Guidelines did not name the sponsor.

RESPONSE

Abbott submitted that the complaint regarding the "Medical News Alert" was essentially similar to the previous complaint and referred to its response in Case AUTH/669/1/98.

With regard to the "Community Management Guidelines for Influenza in Adults", Abbott explained that the Guidelines were formulated by the Community Infection Awareness Group which was not influenced directly by Abbott. Although Abbott sponsored the formation of the group of recognised specialists in the field, their conclusions were free from any editorial direction from Abbott. The Guidelines set out to be a genuine, practical document to assist general practitioners in the treatment of a predicted influenza epidemic and as such discussed the use of a number of treatments which included clarithromycin, amoxycillin, co-amoxiclav, cefuroxine and erythromycin. In recognition of the usefulness of the

document, GP Magazine included laminated copies for distribution within its publication free of charge because of the sound educational content and would not have done so if the document was a deliberate attempt at expanded or subliminal advertising.

The company accepted that the method of sponsorship of the Community Infections Awareness Group, although not the final Guidelines *per se*, should have been disclosed somewhere and agreed to ensure that this was done in all similar documents in the future.

The company did not accept the complainant's accusation of dishonest company practices. The absence of prescribing information on the "Medical News Alert" and the absence of a sponsorship declaration for the Community Infections Awareness Group were oversights on the part of the company. The documents themselves were not factually inaccurate or misleading in their medical content. From a clinical standpoint the company considered it had and was making a helpful contribution to the efficacy of treatment of complicated influenza, so the company was not in breach of medical and ethical standards in this regard. The company accepted that the Guidelines were in breach of Clauses 9.9 and 10.1 of the Code.

PANEL RULING

The Panel considered that its rulings in Case AUTH/669/1/98 regarding the "Medical News Alert" also applied in Case AUTH/680/1/98. The Panel therefore ruled breaches of Clauses 4.1 and 10.1 of the Code.

The Panel examined the Guidelines. The impression from the material was that the Community Infections Awareness Group was an independent group. This was not so. The Group had been established by Abbott. This fact had not been disclosed. The Panel therefore ruled a breach of Clause 9.9 of the Code. The Panel noted that the Guidelines had been distributed free of charge by GP magazine. However there was no indication of who had paid for the production of the laminated card. The Panel considered that it was likely that Abbott had paid those costs.

The Panel considered that the Guidelines in effect promoted clarithromycin for treatment of bacterial respiratory infections. Prescribing information should have been included. A breach of Clause 4.1 of the Code was ruled.

The Panel considered that the distribution of Guidelines constituted disguised promotion and a breach of Clause 10.1 of the Code was ruled.

Complaints received

Case AUTH/669/1/98	**21 January 1998**
Case AUTH/680/2/98	**23 February 1998**
Cases completed	**15 April 1998**

CASE AUTH/670/1/98

GENERAL PRACTITIONER v NAPP

Ticking promotional item

A general practitioner complained about a promotional item for Zanidip which had been included in Pulse by Napp. It took the form of a small four page card which made a ticking noise when it was unsealed and opened. A number of colleagues had mentioned to the complainant that it was an inappropriate means of advertising due to its association with explosive devices. It was particularly disappointing that such a device had been used when a company had previously been found in breach of the Code for using a similar means of catching a doctor's attention.

The Panel noted that in 1994 it had ruled that the use of a device which made the sound of a beating heart failed to recognise the special nature of medicines and the professional standing of the recipients and was in breach. Electronic devices were now more commonplace than they had been then but the Panel considered that it was bound by the precedent and ruled a breach of the Code.

A general practitioner complained about a small promotional item for Zanidip distributed by Napp Laboratories Limited. Napp although not a member of the ABPI had nevertheless agreed to comply with the Code. The promotional item was in the form of a card consisting of 4 pages which made a ticking noise when it was unsealed and opened. The item had been sealed and then loosely inserted into an unsealed transparent pocket attached to the bottom right hand corner of the front page of Pulse of 17 January 1998. Behind the transparent pocket was a black panel with the word "TICKING" repeated over and over and the statement "To find out what's ticking in hypertension see page 14". The promotional item itself made the same statement. A two page advertisement for Zanidip appeared on pages 14 and 15 of the journal. The item bore no prescribing information.

COMPLAINT

The complainant said that a number of general practitioner colleagues had mentioned this promotional item to him as an inappropriate means of advertising due to its association with explosive devices. One colleague had gone so far as to dissect the contents and had assured the complainant that it would be ideal for detonating a letter bomb. It was particularly disappointing that such a device had been used when a company had already been found in breach of the Code for using a similar means of catching a doctor's attention.

RESPONSE

Napp stated that on 12 January it had launched a new product indicated for mild to moderate hypertension

called Zanidip tablets. One of the key straplines for the Zanidip launch campaign was "74 and still ticking". It was with this strapline in mind that the ticker was devised as a striking promotional aid. Napp intended the ticker to act as a reminder for health professionals so that they might associate the new brand with its correct indication. Feedback suggested that this had been achieved.

In preparing for the distribution of the ticker Napp took considerable care to ensure its appropriateness and acceptability. It consulted a number of health professionals for their reaction to the ticker and none of them found it at all objectionable. Napp also obtained specific clearances from the carrier importing the devices, the Royal Mail and the editorial board of Pulse. In accordance with advice received, Napp ensured that the ticker was sealed and carefully attached to Pulse so that it would not go off inadvertently.

The ticker was attached to the 17 January 1998 issue of Pulse which was distributed to approximately 43,000 health professionals. As of 3 February Napp had received ten negative reactions. On the other hand, it had also had, via its sales force, a substantial positive response from health professionals who had viewed the ticker as a thought provoking and imaginative way of promoting a medicine. Napp was therefore surprised and disappointed to receive a complaint under the Code.

It had been alleged that the ticker was an "inappropriate means of advertising due to its association with explosive devices". The complaint went on to state that "One colleague has gone as far as to dissect the contents and assures me that it would be ideal for detonating a letter bomb". Napp's response to this was:

- It was obvious from the surrounding material and, in particular, the strapline "74 and still ticking" that the ticker was intended to be associated with the human heartbeat.
- These devices were now commonplace, particularly in greeting cards.
- The Royal Mail did not associate the ticker with an explosive.
- Whether the ticker was ideal for detonating explosive devices was a matter of speculation. Napp was not an expert in such matters. Clearly, many ordinary items or materials might be adapted for illegal purposes but Napp found it hard to believe that this device was any more useful for detonating a bomb than a clock, watch or all the similar devices contained in greeting cards which were on the shelf of every high street newsagent.

The Authority had suggested that Napp refer to the provisions of Clause 9.1 of the Code. The supplementary information to Clause 9.1 gave some further guidance on what might be considered to be unacceptable under this clause. The examples cited concerned the use of nudity or sexual imagery, "teaser" advertising, prescription rubber stamps and pre-printed product specific prescription forms. While these examples might not be an exhaustive list, they provided indicative examples of where to draw the line. Napp submitted that the ticker had nothing in common with those examples and, given the positive views of the various health professionals whom it consulted, Napp did not believe that it had failed to recognise the professional standing of its audience and did not accept that this item contravened Clause 9.1 of the Code.

Napp noted that the complainant referred to a similar matter four years ago (Cases AUTH/106/1/94 *et al*) and that the Panel in its ruling then stated that devices such as Napp's ticker "were not per se unacceptable under the Code". Those cases to a degree followed an earlier case (Case AUTH/82/10/93) in which the Panel ruled that "... there was no objection to the use of a battery powered microchip device as such ...". The breach in that case concerned the message on the chip, not the chip itself.

When comparing the current case to the cases four years ago the Authority should also be aware that Napp's ticker did not activate in the post. Napp carefully tested its acceptability in advance and the adverse comments it had received appeared to be only a tenth of those received in the previous cases.

In summary, Napp took great care to ensure that the ticker would be acceptable to the full range of health professionals to whom it was sent. Napp believed that the distribution of this device in Pulse magazine recognised the professional standing of the audience and did not contravene Clause 9.1 of the Code. Napp suggested that the views of the complainant were not representative of health professionals generally.

PANEL RULING

The Panel noted that there had been a similar matter involving a four page mailing (Cases AUTH/106/1/94 *et al*. Six complaints had been received). The mailing included an electronic device which, when the mailing was opened out, made a noise similar to that of the human heart. The mailing itself contained information relating to the role of beta blockers in managing cardiovascular disease. The Panel had considered that the use of the device in the mailing failed to recognise the special nature of medicines and the professional standing of the recipients and ruled a breach of Clause 9.1 of the Code. Turning to the case now before it the Panel noted that electronic devices were now more commonplace in greeting cards etc than they had been when the previous cases were considered. The Panel nonetheless considered that it was bound by the precedent set. The Panel considered that the Zanidip item failed to recognise the professional standing of the recipients and ruled a breach of Clause 9.1 of the Code.

In the Panel's view the item constituted an advertisement in the form of a loose insert. Accordingly the item should have included prescribing information for Zanidip and the Panel requested that Napp be advised of its views in this regard.

The Panel considered that the black panel to which the transparent pocket holding the item had been attached was clearly linked to the promotion of Zanidip. The word "TICKING" was repeated over and over and there was a statement which referred the reader to the Zanidip advertisement on page 14 of the journal. In the Panel's view the black panel to which the item had been attached should have fulfilled the requirements for either an advertisement or an abbreviated advertisement for

Zanidip. The Panel requested that Napp be advised of its views in this regard.

The Panel noted that Clause 6.4 of the Code stated that no issue of a journal might bear advertising for a particular product on more than three pages. The Panel considered that the three page allowance had been taken up by the black panel and the two page advertisement. The Panel noted, however, that the relevant issue of Pulse also contained a loose insert for Zanidip which took the form of an envelope containing a "Dear Doctor" letter, a six page mailing, the Zanidip summary of product characteristics and a reply paid card. The supplementary information to Clause 6.4 stated that advertisements in the form of loose inserts counted towards the three pages allowed. A summary of product characteristics or a data sheet was permitted as an insert in addition to the three pages of advertising.

In the Panel's view Napp had exceeded the limit on journal advertising as set out in Clause 6.4 of the Code. The Panel requested that Napp be advised of its views in this regard.

Complaint received 21 January 1998

Case completed 1 May 1998

CASE AUTH/672/1/98

SMITHKLINE BEECHAM v BOEHRINGER INGELHEIM

Mobic advertisement

SmithKline Beecham made a number of allegations about a journal advertisement for Mobic issued by Boehringer Ingelheim. The advertisement featured a woman in evening dress standing on a dais with her arms outstretched. The word "here" was superimposed in white next to all the major joints of the woman's body, ie shoulder, elbow and hip etc. The words "LESS HERE" appeared in red over the woman's stomach/intestine area.

The statement "Deep down, all NSAIDs would like to work like this" appeared as the main heading. In the Panel's view, this could be seen as a description of the goal of NSAID therapy and not, as alleged, that it implied that Mobic had a superior mode of action to other NSAIDs. The Panel noted that the statement appeared above claims for Mobic and might also be viewed as implying that all NSAIDs would like to work like Mobic. On balance, the Panel did not consider that there was an implication that Mobic had a superior mode of action to other NSAIDs and ruled that there was no breach of the Code. The statement "Mobic represents a real development in the everyday treatment of patients with osteoarthritis" appeared immediately below the above statement. The Panel considered that it was misleading and ruled a breach of the Code. It did not clearly reflect the summary of product characteristics for Mobic. In osteoarthritis Mobic was only licensed for the short term symptomatic treatment of acute exacerbations whereas other NSAIDs appeared to be licensed simply for the treatment of osteoarthritis. The claim was too general.

The claim "With a reduction in side effects nobody needs" was ruled not to be in breach of the Code. It had been accepted in a previous case, Case AUTH/583/7/97, that there was clinical evidence to show an improved GI side effect profile for Mobic and the Panel did not accept the allegation that it was a hanging comparison.

The claim "Powerful in the right places" was alleged to be unsubstantiated but the Panel ruled that it was not in breach. It was a strong claim but on balance the Panel considered that it was not unacceptable. The Panel did not consider that the words "LESS HERE" constituted a hanging comparison and ruled no breach in that regard. It was clear that the words referred to the fact that it was preferable for NSAIDs to be effective in the joints but to have less effect on the GI tract.

SmithKline Beecham Pharmaceuticals UK made a number of allegations about a journal advertisement for Mobic (meloxicam) (ref MOB 0021a) issued by Boehringer Ingelheim Limited which had appeared in Pulse on 31 January 1998.

The advertisement was a two page advertisement. The left hand page featured a black and white photograph of a woman in evening dress standing on a dais with her arms outstretched. Superimposed on the photograph, in white, was the word "here" which appeared next to all of the major joints of the woman's body ie shoulder, elbow, hip etc. The words "LESS HERE" appeared in red over the woman's stomach/intestine area. The right hand page was headed "Deep down, all NSAIDs would like to work like this" and gave information about the use of Mobic in osteoarthritis. The prescribing information appeared across the bottom of both pages.

1 "Deep down, all NSAIDs would like to work like this"

This statement appeared on the right hand page as the main heading to the copy.

COMPLAINT

SmithKline Beecham believed this statement strongly implied that Mobic had a superior mode of action to other NSAIDs. This was a somewhat misleading statement as SmithKline Beecham did not consider that there was sufficient comparative clinical data to support it. In particular, the cited study, MELISSA, had a treatment period of only 28 days. Consequently, it did not sufficiently reflect the chronic nature of osteoarthritis (OA) and the need for long term NSAID therapy in this condition. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Boehringer Ingelheim stated that given the image "here" repeated next to joints in the illustration and "LESS HERE" over the gastrointestinal area, the statement

clearly reflected that which all would wish to see. Namely that an NSAID should be perceived as effective in the various joints that might be affected in osteoarthritis (OA) or rheumatoid arthritis (RA) while having less effect on the gastrointestinal (GI) tract. The available epidemiological data (Langman *et al* (1994)) confirmed that NSAIDs varied in their propensity for adverse GI effects. It was therefore self-evident that an NSAID with improved tolerability profile would wish to be perceived as being effective in the arthritic joint while having less symptomatic adverse effects on the GI tract and particularly the stomach.

There was no reason to suppose from the advertisement nor from the literature that Mobic would be superior in terms of beneficial effect to other NSAIDs. On the contrary those knowledgeable in the field, including most GPs, would expect that NSAIDs approved for prescription were effective as to symptomatic inflammation in the joints. Superior efficacy was neither claimed nor implied. Indeed Boehringer Ingelheim's data confirmed equivalence with respect to efficacy with other frequently prescribed NSAID products.

Boehringer Ingelheim therefore rejected the allegation that the advertisement was misleading with respect to efficacy or mode of action. Further, neither the headline nor the illustration were descriptive of the properties of Mobic. Boehringer Ingelheim therefore denied any breach of Clause 7.2.

PANEL RULING

The Panel examined the advertisement and considered that the illustration on the left hand page was being used to demonstrate features of NSAID treatment that all treatments would like to have, ie effective on the joints without causing GI problems. The statement in question headed the right hand page and copy below included claims that Mobic represented "... a real development in the everyday treatment of patients with osteoarthritis", "The efficacy your patients need, where they need it." and "With a reduction in unwanted effects that nobody needs". The final statement in this section was "That is why we believe you should let your patients experience the therapeutic performance of Mobic.".

In the Panel's view the statement "Deep down all NSAIDs would like to work like this" could be viewed in conjunction with the illustration on the left hand page and be seen as a description of the goal of NSAID therapy. The Panel noted that the statement appeared above claims for Mobic and might also be viewed as implying that all NSAIDs would like to work like Mobic. There was data to support an improved GI side effect profile with Mobic compared to certain NSAIDs. There was no implication that other NSAIDs did not meet the criteria. On balance the Panel did not consider that there was an implication that Mobic had a superior mode of action to other NSAIDs. The statement was not misleading as alleged. The Panel therefore ruled no breach of Clause 7.2 of the Code.

2 "Mobic represents a real development in the everyday treatment of patients with osteoarthritis"

This claim appeared immediately below the statement in point 1 above.

COMPLAINT

SmithKline Beecham noted that Mobic was licensed for only the short term management of OA. This was not made clear in the advertisement at all. Furthermore, reference to "everyday treatment of patients with osteoarthritis" was misrepresentative of the current restriction on its licensed use in OA. A breach of Clause 7.2 of the Code was alleged.

RESPONSE

Boehringer Ingelheim stated that SmithKline Beecham was not correct regarding its view that Mobic was licensed for "only the short-term management of OA". The SPC for Mobic stated that Mobic was approved for the "short-term management of symptomatic OA" and "the long-term management of symptomatic RA (rheumatoid arthritis)".

These statements taken from the SPC for Mobic related to the clinical advice that was standard in the modern era for each of these indications in the interests of efficacy and the protection of the GI tract. They did not relate to a specific duration of treatment but to a medical judgement as to when treatment might reasonably be discontinued. "... everyday treatment of patients with osteoarthritis" related to present clinical opinion that OA should be treated on a symptomatic basis but not on a continuous daily basis because of the known risks of serious GI adverse event particularly in the elderly population. Thus the licensed indication in OA for Mobic was not a restriction on its use but was written to conform with current clinical and regulatory thinking on NSAID therapy. The data in support of Mobic included short and long term treatment in both these major indications and now most recently the long term treatment of ankylosing spondylitis. Thus NSAIDs in general and Mobic in particular were indicated for arthritic conditions in which anti-inflammatory action was required. Mobic was therefore to be used as any other NSAID and this use did not require any qualifying statement in the advertising. A further point on this complaint was the definition of everyday, meaning commonplace or unexceptional rather than the complainant's interpretation of "day after day without omission".

Boehringer Ingelheim refuted any breach of Clause 7.2 of the Code.

PANEL RULING

The Panel noted that the Mobic SPC stated that the product was indicated for the "short-term symptomatic treatment of acute exacerbations of osteoarthrosis". The Panel compared the indications for various NSAIDs (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998-99). The Panel noted that SmithKline Beecham's product, Reliflex, was indicated for treatment of osteoarthritis and rheumatoid arthritis requiring anti-inflammatory and analgesic treatment. Tenoxicam was indicated for the relief of pain and inflammation in osteoarthritis and rheumatoid arthritis. Etodolac was indicated for acute or long term use in rheumatoid arthritis and osteoarthritis. The Panel noted that there was a difference in the indications for the various NSAIDs. In terms of osteoarthritis Mobic was

only licensed for the short term symptomatic treatment of acute exacerbations whereas other NSAIDs appeared to be licensed for simply the treatment of osteoarthritis. The Panel did not consider that the advertisement clearly reflected the Mobic SPC instructions with regard to osteoarthritis. The claim was too general given the statement in the SPC. The Panel therefore ruled that the claim was misleading in breach of Clause 7.2 of the Code.

3 "With a reduction in unwanted effects that nobody needs"

COMPLAINT

SmithKline Beecham alleged that this claim was not substantiated and was in breach of Clause 7.3. Furthermore, it was in breach of Clause 7.2 as it constituted a hanging comparison.

RESPONSE

Boehringer Ingelheim disputed the claims of SmithKline Beecham as to substantiation and hanging comparisons. Boehringer Ingelheim's data very clearly were supported by references which confirmed that in both the short and long term there was a reduction in GI side effects, ie unwanted or unneeded effects. The cited reference was in the public domain, with others pending publication. The reduction in GI side effects seen when Mobic was compared with the commonly prescribed NSAIDs, diclofenac, naproxen and piroxicam, was indisputable given a very large clinical trials database already submitted to the European Reference Member State. There was no lack of substantiation for the claim nor support for the allegation of a "hanging comparison".

Boehringer Ingelheim refuted breaches of Clauses 7.2 and 7.3.

PANEL RULING

The Panel noted that in a previous case, Case AUTH/583/7/97, the Panel had accepted that there was data from the study by Distel *et al* to support an improved GI tolerability with Mobic compared to standard doses of well established NSAIDs (piroxicam, diclofenac slow release and naproxen). The case had gone to appeal and the Appeal Board had noted that there was clinical evidence to show an improved GI side effect profile for Mobic.

Turning to the case now before it, the Panel examined the material provided by Boehringer Ingelheim to substantiate the claim. It noted that the material supplied had also been used to support claims in the previous case. The Panel noted that the Appeal Board had accepted there was a reduction in GI events with Mobic. The Panel therefore ruled that no breach of Clause 7.3 of the Code.

The Panel did not accept that the claim constituted a hanging comparison. The Panel therefore ruled no breach of Clause 7.2 of the Code.

4 "Powerful in the right places"

COMPLAINT

SmithKline Beecham alleged that this claim was unsubstantiated and was in breach of Clause 7.3.

RESPONSE

Boehringer Ingelheim stated that SmithKline Beecham's allegation was mystifying since the product licence and SPC confirmed that Mobic was licensed for the treatment of OA, RA and ankylosing spondylitis. This was unequivocal evidence of the efficacy of Mobic in the places expected of an NSAID, namely inflamed joints. Powerful was a non-quantitative term implying significant effect but was neither a superlative nor comparative term that might require further substantiation.

Boehringer Ingelheim refuted any breach of Clause 7.3.

PANEL RULING

The Panel considered that the claim "Powerful in the right places" was a strong claim but considered that on balance it was not unacceptable. No breach of Clause 7.3 of the Code was ruled.

5 "LESS HERE"

COMPLAINT

SmithKline Beecham alleged that, as a hanging comparison, this phrase breached Clause 7.2 and, furthermore, it was unsubstantiated, contravening Clause 7.3.

RESPONSE

Boehringer Ingelheim stated that with regard to the alleged hanging comparison, it was difficult to understand the allegation given the context of the advertisement which suggested "effect" in the joints and "less effect" in the GI tract. Again the data amply supported the often repeated desire for an NSAID with analgesic and anti-inflammatory effect in the joints and less effect in the GI tract. All the data available for Mobic, whether from spontaneous reports or the clinical trials database, supported the claim of effect relevant for inflamed joints and less effect on the GI tract than with respect to the NSAIDs most commonly prescribed in the UK and Continental Europe.

Boehringer Ingelheim therefore denied any breach of the Code.

PANEL RULING

The Panel examined the illustration and considered the words "LESS HERE" did not constitute a hanging comparison. In the Panel's view it was clear that the words "LESS HERE" referred to the fact that it was preferable for NSAIDs to be effective in the joints but to have less effect on the GI tract. The Panel did not consider that the phrase was unacceptable and no breach of the Code was ruled.

Complaint received 27 January 1998

Case completed 3 June 1998

CASE AUTH/673/1/98

ZENECA PHARMA v SERVIER

Coversyl leavepiece

Zeneca Pharma complained about a heart failure leavepiece for Coversyl (perindopril) issued by Servier, alleging that it misled doctors to believe that lisinopril (Zeneca's product Zestril) was dosed twice daily and misled with respect to the cost of treatment with lisinopril insofar as it used an incorrect dosage regimen to artificially inflate the cost of lisinopril in comparison with perindopril. It was further alleged that the non-proprietary name, perindopril, was in a type size smaller than the requisite 10 point.

The Panel noted that the Zestril data sheet stated that it was to be administered in a single daily dose and that the usual maintenance dose in congestive heart failure was 5-20mg. The cost comparison chart, however, gave the cost on the assumption that lisinopril was given in daily doses of 5, 10 or 20mg, or in divided doses of 2.5, 5 or 10mg twice daily. Each of the divided doses of lisinopril was more expensive than the usual maintenance dose of perindopril. Only the highest once daily maintenance dose of lisinopril was more expensive than perindopril. The Panel considered that the chart gave the impression that lisinopril treatment was more expensive than perindopril and this was not so. The Panel considered that by including the cost of twice daily lisinopril the chart was misleading and it was ruled in breach. A breach was also ruled because the size in which the non-proprietary name appeared adjacent to the most prominent display of the brand name Coversyl was less than the requisite 10 point bold.

Zeneca Pharma submitted a complaint about a Coversyl (perindopril) leavepiece (ref: 98.COCC101) produced by Servier Laboratories Ltd. The leavepiece was distributed to general practitioners and hospital doctors by Servier representatives. The leavepiece contained a cost comparison bar chart headed "Daily Doses and 28 Day Cost of Ace Inhibitors in Heart Failure" which compared the cost of the usual maintenance dose of perindopril (4mg od) with three other ACE inhibitors including lisinopril. Six different doses of lisinopril were given, 2.5, 5 and 10mg bd and 5, 10 and 20mg od. The date of preparation of the leavepiece was August 1997.

COMPLAINT

Zeneca stated that it had reason to believe that Servier had been leading general practitioners to believe that lisinopril ('Zestril': Zeneca and 'Carace': Du Pont) was dosed twice daily. Lisinopril was in fact dosed once daily for all indications. It had never been licensed for twice daily dosing. Zeneca stated that it had complained to Servier in April 1995, October 1996 and September 1997. On each occasion it was given an assurance that Servier was not claiming lisinopril to be a twice daily medicine. Zeneca had now obtained a copy of the general practitioner leavepiece at issue which clearly indicated to the reader that lisinopril was dosed once and twice daily.

Zeneca stated that in view of its complaints to Servier over the last two and a half years, it was very disappointed to note that the leavepiece was prepared in the month preceding Servier's latest denial that it had been suggesting lisinopril to be a twice daily medicine.

Zeneca therefore alleged that the leavepiece breached Clause 7.2 of the Code on two counts. Firstly it misled doctors to believe that lisinopril was dosed twice daily and secondly it misled doctors with respect to the cost of treatment with lisinopril insofar as it used an incorrect dosage regimen to artificially inflate the cost of lisinopril for direct comparison with perindopril.

Zeneca provided data sheet texts prepared July 1995, January 1997, April 1997 and the current data sheet prepared December 1997.

Zeneca also pointed out that the approved name, perindopril, adjacent to the most prominent display of the brand name, Coversyl, was in a type size smaller than 10 point. The company therefore further alleged a breach of Clause 4.2 of the Code.

RESPONSE

Servier stated that the leavepiece included a comparison chart for the cost of ACE inhibitors in heart failure. The cost of various doses and dosages of ACE inhibitors were listed. For lisinopril, this included once daily and twice daily dosages. Servier accepted that only once daily dosages should appear on this piece and that inclusion of twice daily was misleading. Servier therefore acknowledged that this piece was in breach of Clause 7.2 of the Code. Servier also accepted a breach of Clause 4.2 of the Code. Servier confirmed that the piece at issue was no longer in use.

PANEL RULING

The Panel noted that the earlier Zestril data sheet texts of July 1995 (which had appeared in the 1996-97 ABPI Data Sheet Compendium) and January 1997 had been silent on the issue of whether the usual maintenance dose of Zestril (5-20mg) should be given as a single daily dose or in divided doses. The later data sheet text of July 1997 (which was in the ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998-99) and the current data sheet (prepared December 1997) both clearly stated under "Dosage and Administration" that "Zestril should be administered in a single daily dose".

The Panel noted that the Zestril data sheet stated that the product was to be administered in a single daily dose and that the usual maintenance dose in congestive heart failure was 5-20mg. The cost comparison chart, however, gave the cost of such doses on the assumption that they could be given either as single daily doses of 5, 10 or 20mg, or in two daily doses of 2.5, 5 or 10mg. The Panel noted that the cost of twice daily lisinopril was much greater than the same total daily dose given once daily. The cost of lisinopril 20mg a day was £23.66 if given as 10mg bd but only £13.38 if administered as a single daily dose. Each of the doses of lisinopril if given in divided doses were more expensive than the cost of the usual maintenance dose of perindopril (Coversyl) which was

£12.74. Only the highest usual maintenance dose of Zestril (20mg) at £13.38 was more expensive than perindopril if a once daily dosing schedule was employed. The Panel noted that on the whole the chart gave the impression that lisinopril treatment was more expensive than perindopril. This was not so. The Panel considered that by including the cost of twice daily lisinopril the cost comparison chart was misleading and a breach of Clause 7.2 of the Code was ruled.

The Panel noted that the brand name "Coversyl 4mg" appeared twice on the front cover of the leavepiece in logo type. Above each mention of the product name was "perindopril" in a type size so small that the Panel considered that it was difficult to read. The Panel noted that Clause 4.2 of the Code listed the component parts of the prescribing information and, in addition, stated that the non-proprietary name or a list of active ingredients must appear immediately adjacent to the most prominent display of the brand name in not less than 10 point bold or in a type size which occupied a total area no less than that taken by the brand name. Clause 4.1 of the Code stated that the information listed in Clause 4.2 must be provided. Failure to do so would therefore be a breach of Clause 4.1 and not of Clause 4.2. Servier had failed to print the non-proprietary name in the correct type size. The Panel therefore ruled a breach of Clause 4.1 of the Code.

Complaint received **28 January 1998**

Case completed **30 March 1998**

CASE AUTH/674/2/98 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v SCHWARZ PHARMA

Promotion of Tylex

A general practitioner complained about a Tylex leavepiece issued by Schwarz Pharma. The leavepiece included a cost comparison chart of the daily cost of six leading brands of analgesic at maximum daily dose. The complainant alleged that the chart was misleading. It appeared to show Tylex (co-codamol 30/500) to be considerably cheaper at 69 pence daily than two strengths of co-dydramol at 87 pence and £1.07 daily respectively. The vast majority of co-dydramol was prescribed generically as co-dydramol tablets 10/500 and the cost was approximately 11p for the maximum daily dose. There were brands of co-dydramol at the strength and price shown but these were not often prescribed and at a casual glance it would be assumed that the chart referred to "ordinary" co-dydramol.

The Panel noted that a price comparison should be made on the basis of the equivalent dosage requirement for the same indication. Tylex was indicated for the relief of severe pain and the leavepiece discussed the relief of severe pain. The Panel noted that five of the six medicines on the chart, including the two strengths of co-dydramol, were indicated for moderate to severe or severe pain but queried the inclusion of the sixth, meptazinol, which was indicated only for moderate pain. The Panel noted that co-dydramol 10/500, which was available only as a generic, was indicated for mild to moderate pain and considered that on the basis of its indications it was acceptable not to include it in the price comparison chart. The Panel noted that the chart was headed "Cost per day of leading brands at maximum daily dosages". The Code prohibited the use of other companies' brand names without their consent. The Panel considered that the leavepiece was sufficiently clear in its description of the co-dydramol products included. No breach of the Code was ruled.

A general practitioner complained about a Tylex leavepiece (ref 339/395) from Schwarz Pharma Limited. The leavepiece included a cost comparison chart of the daily cost of six leading brands of analgesics at maximum daily dose. Tylex (codeine phosphate 30mg and paracetamol 500mg ∫ co-codamol 30/500) was the least expensive brand at 69 pence daily. Two co-dydramol products (dihydrocodeine/paracetamol) were included in the chart, co-dydramol 20/500 at 87 pence daily and co-dydramol 30/500 at £1.07 daily.

COMPLAINT

The complainant alleged that the chart was misleading. The complainant noted that the chart compared Tylex capsules with other analgesics and appeared to show Tylex to be considerably cheaper than two strengths of co-dydramol. The vast majority of co-dydramol was prescribed generically as co-dydramol tablets 10/500. The cost was approximately 11p for the maximum daily dose. The complainant acknowledged that the chart was technically correct, as there were brands of co-dydramol at the strength and price shown but these were not often prescribed and a casual glance would assume that the chart referred to "ordinary" co-dydramol. This was borne out by the representative, who told the complainant that he was the first doctor who had ever queried the chart.

The complainant alleged that the chart was in breach of the Code and referred to the supplementary information to Clause 7.2. Reference was also made to the supplementary information to Clause 15 which stated that "Representatives must not make claims or comparisons which are in any way inaccurate, misleading, disparaging, in poor taste etc ...".

The complainant stated that he was used to pharmaceutical marketing being economical with the truth but considered that this case was far worse and was in fact deliberately misleading.

RESPONSE

Schwarz stated that it appeared that the representative had not made any claim or comparison that was not in the printed material. This being the case, it was an objection to the leavepiece under Clause 7.2 that should be considered.

Schwarz stated that having reviewed the promotional

item in question, the data contained in the chart was as the complainant stated "... technically correct as there were brands of co-dydramol at that strength and price ...".

Schwarz stated that there was no intention to deceive and considered there was no deception.

Schwarz agreed that clarity could be helped by using brand names to label the two bars representing the prices of the strengths of co-dydramol. However, this could not be actioned as it was prohibited by Clause 7.10 of the Code. Accepting this limitation the company considered the price comparison chart to be accurate, balanced, fair and that Clause 7.2 had not been breached.

PANEL RULING

The Panel noted that the supplementary information to Clause 7.2 (price comparisons) stated that a price comparison should be made on the basis of the equivalent dosage requirement for the same indication. The Panel noted that Tylex was indicated for the relief of severe pain. The leavepiece discussed the relief of severe pain. The Panel noted that the price comparison chart listed six medicines, five of which, including the two strengths of co-dydramol, were indicated for moderate to severe or severe pain (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1998-99). The Panel queried the inclusion of the sixth product, meptazinol, which was indicated only for moderate pain. The Panel noted that co-dydramol 10/500 (available only as a generic) was indicated for mild to moderate pain (ref MIMS January 1998). The Panel considered that on the basis of indications it was acceptable not to include co-dydramol 10/500 in the price comparison chart.

The Panel noted that the chart was headed "Cost per day of leading brands at maximum daily dosages". Clause 7.10 of the Code prohibited the use of the brand names of other companies' products unless the prior consent of the proprietors had been obtained. The Panel considered that the material was sufficiently clear in its description of the co-dyramol products included and that the costs were based on the maximum daily dose of branded products. No breach of Clause 7.2 of the Code was ruled.

As there was no complaint that the representative had said anything other than what appeared in the leavepiece, the Panel decided that it was not necessary to consider the alleged breach of Clause 15.2 as this was covered by its ruling of no breach of Clause 7.2.

Complaint received **2 February 1998**

Case completed **6 May 1998**

CASE AUTH/675/2/98

NO BREACH OF THE CODE

NURSE v GLAXO WELLCOME

Crusaid advertisement

An article in Positive Nation referred to a Crusaid advertising campaign to encourage gay men to test for HIV so that they could take advantage of new drug treatments. The article said that a series of advertisements headed "Try this HIV test" in Axiom magazine had been paid for by Glaxo Wellcome which manufactured AZT, 3TC and a wide range of other HIV medicines. The campaign's creators acknowledged Glaxo Wellcome's involvement but said that the company took no part in writing the advertisements and was contributing only a tiny percentage of the campaign's budget. It was stated in the article that Glaxo Wellcome could be in breach of rules outlawing pharmaceutical companies from advertising their products direct to the public and that the company faced investigation by the Authority. At the time that the article was published no complaint had been received about the advertising and the Authority was unaware of it.

A complaint was subsequently received from a nurse who said that he had been concerned to read the article. The campaign had been reported on BBC 1 News and BBC Radio 4's Today programme. He knew people with HIV and how important completely impartial information was to them about the medicines they used, or might use, to fight their virus. People who were HIV positive associated Glaxo Wellcome with AZT and advertising of this medicine by the back door could not be allowed.

The Panel noted that none of the advertisements mentioned Glaxo Wellcome. Glaxo Wellcome had provided a donation to Axiom magazine for advertising space and a donation to Crusaid for general funding which would include the HIV testing campaign. It had had no editorial input to the campaign. The company was not the only source of funding for either Axiom or Crusaid. The cost of the campaign was much greater than Glaxo Wellcome's donations. Glaxo Wellcome was not the only company involved in the area of HIV treatment. The advertisement referred to new treatments but did not mention any specific medicines, classes of medicines or pharmaceutical companies. The Panel did not consider that the advertisement was in effect an advertisement for AZT as alleged and ruled that there had been no breach of the Code.

An article in the February 1998 issue of Positive Nation referred to a Crusaid advertising campaign to encourage gay men to test for HIV so that they could take advantage of new treatments. The article said that a series of advertisements headed "Try this HIV test", to appear in Axiom magazine which was distributed free in gay venues and clinics, had been paid for by Glaxo Wellcome, the firm which manufactured AZT, 3TC and a wide range of other HIV medicines. The article stated that the series also appeared in national gay publications where it was funded by the charity Crusaid. The campaign's creators, Camden and Islington Health Authority, acknowledged Glaxo Wellcome's involvement but insisted that the company took no part in writing the advertisements and was contributing only a "tiny percentage" of the campaign's budget. It was stated that Glaxo Wellcome could be in breach of strict industry rules outlawing pharmaceutical companies from advertising their products direct to the public. The article stated that the company faced investigation by the Authority which would want to determine if the advertisement amounted to "drumming up business" for the company's combination therapy medicines.

The Director of the Authority had written to Positive Nation to correct errors in the article. At the time the article was published no complaints had been received about the advertising and the Authority was unaware of it, although one complaint had been received following publication of the article.

COMPLAINT

A state enrolled nurse said that he had been most concerned to read the article regarding the advertising campaign by Crusaid. The campaign had been reported on BBC 1 News and BBC Radio 4's Today programme over Christmas. He had a number of friends and clients with HIV and he knew how important completely impartial information was to them about the medicines they used (or might use) to fight their virus. The complainant knew that Glaxo Wellcome had been a very unpopular company a few years ago among many HIV positive people due to the controversy over AZT. Advertising by the back door of this medicine could not be allowed.

RESPONSE

Glaxo Wellcome UK Limited said that the article contained many inaccuracies and the company was discussing these with the editor directly. A copy of a letter to Positive Nation was provided as was a statement from Crusaid on the article. The inaccuracies within the article implied that Glaxo Wellcome had breached the Code but the company firmly believed that this was not the case.

Information about the testing campaign first came to Glaxo Wellcome's attention in the summer of 1997 when it was initially approached by Axiom magazine regarding support for a campaign in conjunction with Camden and Islington Health Promotion Service (C+IHPS) to raise awareness in the gay community regarding HIV testing. Glaxo Wellcome provided an unrestricted donation to Axiom to allow advertising space for its campaign. It was agreed that C+IHPS' advertisements would be printed on the pages for which Axiom had sought funding. C+IHPS was a part of Camden and Islington Community Health Services NHS Trust. Correspondence relating to this donation was provided.

Independently of the above, Crusaid, a registered charity, had also planned to initiate an HIV testing campaign but subsequently joined with C+IHPS. Crusaid agreed to fund the campaign. Crusaid approached Glaxo Wellcome, amongst others, for financial support. The joint Crusaid and C+IHPS campaign would be publicised in the gay press as well as via gay organisations. The "Try This HIV

Test" campaign was developed in consultation with local HIV testing and treatment services. The draft text was reviewed and supported by other professionals from other HIV organisations.

Glaxo Wellcome committed to, and subsequently provided, an unconditional donation to Crusaid under the Inland Revenue Gift Aid scheme. Details of the donation and the scheme were provided. This donation was for general funding of Crusaid's activities, which would include the aforementioned campaign. Glaxo Wellcome neither sought nor offered editorial input to the campaign. No mention was made in the advertisement of Glaxo Wellcome or other supporters of Crusaid, nor was any mention made of specific HIV therapies or groups of therapies. Similar campaigns from the Health Education Authority and CHAPS (Terence Higgins Trust) had subsequently appeared. Examples of the advertisements from these organisations were provided.

The distribution of the campaign was detailed in a facsimile from C+IHPS which was provided, which also included a commentary upon the campaign planning, aims and its messages and the cost of the campaign.

Glaxo Wellcome listed the licensed therapies available following a positive HIV test, together with their respective licence holders:

Didanosine (ddI) - Bristol-Myers Squibb
Indinavir - Merck Sharp & Dohme
Lamivudine (3TC) - Glaxo Wellcome
Ritonavir - Abbott
Saquinavir - Roche
Zalcitabine (ddC) - Roche
Zidovudine (ZDV / AZT) - Glaxo Wellcome

As the Authority would be aware, HIV disease was of a special nature and several compassionate use programmes were underway for currently unlicensed therapies. The following were products that Glaxo Wellcome was aware of that were currently available via compassionate use programmes:

1592 - Glaxo Wellcome
266 - DuPont Merck
Delavirdine - Pharmacia & Upjohn
Nevirapine - Boehringer Ingelheim
Nelfinavir - Roche

Guidance for the use of the various therapies available was given in the latest British HIV Association (BHIVA) guidelines for the treatment of HIV seropositive individuals. These guidelines reflected current understanding that early treatment before the onset of symptoms was beneficial and should be offered. Additionally, they discussed that the choice of treatment required an individual approach.

Glaxo Wellcome was a leading provider of HIV related therapies, and was interested in exploring initiatives with charities and organisations that supported people with HIV and AIDS. Crusaid was one such organisation. Crusaid sought to help people with HIV, and their families and carers, to enjoy a better quality of life. In addition to some statutory funding, they raised money through voluntary donations and fund raising activities. Crusaid's mission statement was provided.

In view of the above arrangements, Glaxo Wellcome reiterated its position that it believed that Glaxo Wellcome in its relationship with Crusaid and its "Try This HIV Test" campaign had not breached the Code.

PANEL RULING

The Panel considered that it was not necessarily always acceptable for pharmaceutical companies to make donations to charities and the like. Any conditions attached to such donations would be important factors in deciding their acceptability in relation to the Code.

The Panel had been provided with a copy of the double page advertisement which had featured in the article in the February 1998 edition of Positive Nation. The left hand page of the advertisement was headed "Try this HIV test ..." underneath which was listed a number of questions about HIV and its transmission. Readers were told that if they answered "Yes" to any of the questions now was the time to consider having an HIV test. The right hand page gave information about the treatment of HIV. Information given was that there had been encouraging progress in the treatment of HIV and that to take advantage of the new treatments people needed to know if they were HIV positive. The only way to know this for sure was if a HIV test was taken. The advertisement also stated that there were effective treatments which reduced the level of the virus in blood and which, with long-term use, might delay HIV disease. In addition readers were told that treatment centres might vary in what they recommended and that "New treatments are not cures". The Panel noted that no specific medicines were mentioned. The advertisement acknowledged that the campaign was being run by the Camden and Islington Community Health Service NHS Trust with funding provided by Crusaid which was described as the national fundraiser for HIV and AIDS. If readers required further information the telephone numbers of the Terence Higgins Trust Helpline and the National AIDS Helpline were given. There was no mention of Glaxo Wellcome.

The Panel noted that it had also been provided with a copy of the various advertisements which had comprised the "Try this HIV test" campaign. While all of the advertisements were slightly different the tone of the text remained constant. None of the advertisements mentioned any specific medicines and none mentioned Glaxo Wellcome.

The Panel noted that Glaxo Wellcome had provided a donation to Axiom magazine to allow advertising space for a campaign in conjunction with C+IHPS. The Panel noted Glaxo Wellcome's submission that Crusaid had also planned to initiate an HIV testing campaign but had subsequently joined with C+IHPS. Glaxo Wellcome had given a donation to Crusaid for general funding which would include the HIV testing campaign.

The Panel noted that Glaxo Wellcome had neither sought nor offered editorial input to the campaign. Editorial control remained solely held by C+IHPS. Glaxo Wellcome had been provided with details about the advertisements by way of a facsimile dated 12 February 1998. The complaint had been received prior to that date.

The Panel noted that Glaxo Wellcome was not the only source of funding for either Axiom or Crusaid. The cost of

the campaign was much greater than the donations provided by Glaxo Wellcome.

The Panel noted that Glaxo Wellcome was not the only pharmaceutical company involved in the area of HIV treatment. The advertisement referred to new treatments but did not mention any specific medicines, classes of medicines or pharmaceutical companies. The Panel did not consider that the advertisement provided was in effect an advertisement for AZT as alleged. No breach of Clause 20.1 of the Code was ruled.

Complaint received **4 February 1998**

Case completed **2 June 1998**

CASE AUTH/676/2/98

ASTRA v WYETH

Price comparison in Zoton advertisement

Astra complained about an advertisement for Zoton issued by Wyeth which had appeared in GP. The advertisement was headed "Zoton low price still leaves omeprazole out in cold". The subheading was "Costs per 28 day prescription". The cost of Zoton 15mg was given as £18.95 and the cost of omeprazole 20mg as £30.13, followed by the claim "Saving with Zoton 15mg £11.18" beneath which in smaller lettering was "In maintenance therapy". Astra alleged that the advertisement was unfair and misleading as it compared the lowest maintenance dose of Zoton with the highest maintenance dose of omeprazole.

The Panel noted that the cost comparison given in the advertisement was not put into any clinical context in that it referred only to Zoton 15mg and omeprazole 20mg. In the Panel's view, most readers would assume that this was a simple comparison of licensed doses and that these were the only ones which could be used for maintenance therapy which was not so. From the data sheets it was clear that some patients might be maintained on Zoton 30mg and others on omeprazole 10mg. To compare the cost of the lowest maintenance dose of Zoton with the highest for omeprazole was misleading and the Panel ruled a breach of the Code.

Astra Pharmaceuticals Ltd complained about an advertisement for Zoton (ref ZZOT840/0298) issued by Wyeth Laboratories which had appeared in GP, 6 February 1998.

The advertisement was headed "Zoton low price still leaves omeprazole out in the cold". Below this was the sub-heading "Costs per 28 day prescription" which was referenced to a footnote. Beneath the subheading the cost of Zoton 15mg was given as £18.95 and the cost of omeprazole 20mg was given as £30.13 followed by the claim "Saving with Zoton 15mg £11.18" beneath which in smaller lettering was "In maintenance therapy". The footnote in very small lettering stated "Based on the cost of 28 days' maintenance treatment with Zoton 15mg at Manufacturers' recommended doses; MIMS February 1998 and data on file, Wyeth".

COMPLAINT

Astra stated that it was extremely concerned about the advertisement which it alleged breached Clauses 2 and 7.2 of the Code. The price comparison shown did not compare like with like doses and was therefore unfair and misleading.

The costs were "per 28-day prescription", "in maintenance therapy" for Zoton 15mg and omeprazole 20mg. However, each product was licensed in the maintenance treatment of gastro-oesophageal reflux disease and peptic ulceration with a range of doses. The advertisement compared the lowest maintenance dose of Zoton with the highest maintenance dose of omeprazole.

Licensed daily doses in the maintenance treatment of gastro-oesophageal reflux disease and peptic ulceration were 15mg and 30mg for Zoton, and 10mg and 20mg for omeprazole.

The advertisement compared Zoton 15mg with omeprazole 20mg which were not equivalent. The usual recommended maintenance dose of omeprazole was 10mg; omeprazole 20mg daily was only necessary if symptoms returned.

The cost comparison was the principal message in the advertisement. As this was based on an unfair and misleading comparison of dosages, Astra believed this type of advertising brought the industry into disrepute and hence was in breach of Clause 2.

Astra had written to Wyeth to ask for confirmation that use of the advertisement would cease immediately and that no further similar price comparisons would be made in advertisements or other material. Astra's normal practice was to await the outcome of inter-company dialogue on Code of Practice matters. However, it viewed the Zoton advertisement as a flagrant breach of the Code and on this occasion had brought the matter directly to the Authority.

Astra confirmed that the cost of Losec (omeprazole) 20mg x 28 capsules was £30.13.

RESPONSE

Wyeth stated that this specific advertisement had appeared in GP, Pulse, Doctor and Hospital Doctor from 6 February 1998. The current cost of a 28 capsule pack of Zoton 15mg was confirmed at £18.95.

Wyeth believed that its price comparison of Zoton 15mg with omeprazole 20mg in gastro-oesophageal reflux disease maintenance therapy was both fair and objective. Cost comparisons were appropriate when related to the outcome of the treatments delivered in terms of their achieving the required, similar clinical end points, measured both directly and indirectly where appropriate.

Wyeth's claim was based upon an up-to-date evaluation of the total published evidence of clinical outcomes data in this therapeutic area, comparing the two products at the stated doses. In addition, the clinical outcomes data was further supported by gastric acid suppression data, which was the desired pharmacological end point for this class of medicines.

Clinical outcomes comparison

There was a substantial body of published evidence to show that, in terms of clinical outcome, Zoton 15mg was equivalent to omeprazole 20mg in the maintenance of gastro-oesophageal reflux disease. The objective clinical end point for this disease was the percentage of patients in endoscopic remission at 12 months, following initiation of maintenance therapy with either Zoton 15mg or omeprazole 20mg.

The only direct head to head comparison of 15mg Zoton versus 20mg omeprazole in the maintenance of reflux oesophagitis was Baldi *et al* (1996). Endoscopic remission rates at 12 months showed no statistically significant difference between lansoprazole 15mg and omeprazole 20mg.

Four studies had evaluated the use of lansoprazole 15mg in the maintenance of reflux oesophagitis, with the common endpoint of endoscopic remission rates after 12 months of maintenance therapy. These studies, together with the Baldi study, gave remission rates, after 12 months' maintenance therapy with lansoprazole 15mg, ranging form 69% to 87%. The specific study results were Gough *et al* (1996), 69%; Hatlebakk and Berstad (1997), 72%; Baldi *et al* (1996), 76%; Robinson *et al* (1996), 79% and Poynard *et al* (1995), 86%.

The three studies using omeprazole 20mg in reflux oesophagitis, which assessed endoscopic remission rates after 12 months' maintenance therapy (ie comparable with the studies referenced for lansoprazole 15mg), showed remission rates ranging from 74-89%, specifically Bate *et al* (1995), 74%; Vigneri (1995), 80%; Baldi *et al* (1996), 87% and Dent (1994), 89%.

The results of these two groups of studies showed very similar ranges (lansoprazole 15mg, 69-87%; omeprazole 20mg, 74-89%) in terms of percentage of patients in endoscopic remission at 12 months. These ranges were confirmed by Baldi in the only comparative study, which showed that there was no significant difference between lansoprazole 15mg and omeprazole 20mg in the maintenance of reflux oesophagitis.

Pharmacological end points (acid suppression)

Further evidence of equivalence between Zoton 15mg and omeprazole 20mg was provided by comparative acid suppression studies. These studies demonstrated that Zoton 15mg was equivalent to omeprazole 20mg in terms of acid suppression, as assessed by intragastric pH measurements.

Tolman *et al* (1997) showed that lansoprazole 15mg and omeprazole 20mg increased 24 hour gastric pH and that there was no difference in the percentage of time that gastric pH was >3, 4 and 5. Similarly Seensalu *et al* (1995) showed that the effects on gastric acidity were equivalent for lansoprazole 15mg and omeprazole 20mg.

Dammann *et al* (1997) studied reductions in meal-stimulated acid secretion and showed that on day 5 there was no significant difference between lansoprazole 15mg and omeprazole 20mg in inhibiting meal-stimulated gastric acid secretion.

Blum *et al* (1997) showed that lansoprazole 15mg was equivalent to omeprazole 20mg in terms of acid suppression. He also showed similar percentages of time when the gastric pH was above 3 (64% vs 63%) and above 4 (48% vs 41%).

The above comparative studies showed that in terms of acid suppression lansoprazole 15mg was equivalent to omeprazole 20mg in suppressing intragastric pH.

Wyeth believed that the comparable clinical outcomes evidence, supported by the pharmacological data on acid suppression, fully justified Wyeth's comparison of lansoprazole 15mg with omeprazole 20mg in maintenance therapy. It therefore believed that Wyeth had not breached Clause 7.2 of the Code in making this claim and therefore implicitly a ruling under Clause 2 would be inappropriate.

PANEL RULING

The Panel noted, from data sheets that had been provided, that Zoton and Losec were indicated for a number of acid related disorders of the upper gastrointestinal tract. The cost comparison featured in the advertisement did not specify a particular disorder but referred to maintenance therapy in general.

The Panel noted that for Zoton in the long-term management of gastro-oesophageal reflux disease a maintenance dose of 15mg or 30mg once daily could be used dependent upon patient response. For the prevention of relapse in patients with duodenal ulcer the recommended maintenance dose of Zoton was 15mg daily. Turning to Losec the Panel noted that in oesophageal reflux disease, including reflux oesophagitis, patients could be continued at a dosage of 20mg daily. For the long-term management of acid reflux disease 10mg once daily was recommended, increasing to 20mg if symptoms returned. For the prevention of relapse in patients with duodenal ulcer the recommended dose of Losec was 10mg once daily increasing to 20mg if symptoms returned. Patients at risk, or with a history of recurrent duodenal ulcer, were recommended to take a dose of Losec 20mg daily reducing to 10mg once daily if necessary. The Panel noted, therefore, that dependent upon the particular disorder and individual patient response a maintenance dose of Zoton could be 15mg or 30mg and that of omeprazole could be 10mg or 20mg.

The Panel noted that the cost comparison given in the advertisement was not put into any clinical context in that it referred only to Zoton 15mg and Losec 20mg. In the Panel's view most readers would assume that this was a simple comparison of licensed doses and that these were the only ones which could be used for maintenance therapy which was not so. From the product data sheets it was clear that some patients might be maintained on Zoton 30mg and others on Losec 10mg.

The Panel considered that to simply compare the cost of

the lowest maintenance dose of Zoton with that of the highest maintenance dose of omeprazole was misleading. A breach of Clause 7.2 was ruled. The Panel did not consider that the matter amounted to a breach of Clause 2 and ruled accordingly.

Complaint received 23 February 1998

Case completed 18 May 1998

CASE AUTH/678/2/98

GLAXO WELLCOME v MERCK SHARP & DOHME

Launch of Singulair

Glaxo Wellcome complained about broadcasts on radio and television referring to the launch of Singulair (montelukast) by Merck Sharp & Dohme, including an interview with Merck Sharp & Dohme's Director of Medical Affairs on BBC Radio 5 which, it was alleged, constituted advertising to the public even though the medicine was not specifically named.

The Panel noted that complaints about media items were judged on the material which had been provided by the company or its agents. With interviews with company representatives, a judgement would be made on what the representative had said. The Panel examined the media information pack and video news reel provided by Merck Sharp & Dohme but did not consider that they amounted to advertising to the public or that the information provided was unreasonable. No breach of the Code was ruled in relation to these materials. During the interview with Merck Sharp & Dohme's Director of Medical Affairs, when asked whether most asthma sufferers would be able to go to a doctor and ask to try the new medicine, he had replied "Yes, I mean the ... asthma sufferers should go to their doctor and ask them if they are suitable for this medication. Obviously it won't be suitable for all patients but for the vast majority it may be suitable to control those patients who aren't controlled on their current treatments". In the Panel's opinion this statement would encourage patients to ask their doctors to prescribe a specific medicine and a breach of the Code was ruled.

Glaxo Wellcome UK Limited complained about the content of an interview broadcast on BBC Radio 5 on 9 February 1998 which referred to the launch of montelukast (Singulair) by Merck Sharp & Dohme Limited. Transcripts sent with the letter of complaint also referred to other broadcasts on radio and television and Glaxo Wellcome subsequently made it clear that it wished all of these to be taken into consideration. Some of the transcripts had been marked with asterisks.

The broadcast on BBC Radio 5 consisted of an interview with Dr Richard Tomiak, Merck Sharp & Dohme's Director of Medical Affairs in the UK. The other broadcasts contained interviews and reports from health correspondents, health professionals and the like.

COMPLAINT

Glaxo Wellcome stated that it was very concerned at the content of the interview which it strongly asserted constituted a clear attempt at promoting montelukast (Singulair) to the public, even though the medicine was not specifically named. Glaxo Wellcome stated that it had had concerned general practitioners telling its representatives that this was exactly what had happened and that members of the public had been enquiring about this new medicine from them. As such Glaxo Wellcome believed this interview was a clear breach of Clauses 20.1 and 20.2 and also Clause 2 of the Code and had taken the unusual route of writing direct to the Authority rather than initially to Merck Sharp & Dohme, to try to ensure that further such broadcasts did not take place.

RESPONSE

Merck Sharp & Dohme denied that the media campaign caused any breach of the Code and more specifically it denied breaches of Clauses 20.1, 20.2 and/or Clause 2.

Merck Sharp & Dohme contended that nothing in the coverage of the launch of Singulair amounted to an advertisement to the general public (Clause 20.1). This treatment was the first new class of treatment for asthma in over twenty years. As such it was Merck Sharp & Dohme's contention that it would inevitably attract widespread media attention, and thus it was a genuine "news" story and it believed it had acted responsibly in providing appropriate information about this new therapy. A media information pack and video news reel were provided.

Merck Sharp & Dohme had ensured that the relevant health professionals were informed of the availability of Singulair from 30 January 1998 and the information released to the non-health professional media was embargoed until 9 February 1998. All the press and media releases were reviewed to ensure that the indications for Singulair were entirely consistent with the licence precisely to avoid any suggestion that the information would "... raise unfounded hopes of successful treatment ...".

The press release material clearly emphasised that Singulair was add-on therapy to existing asthma treatments namely, beta agonists and inhaled steroids. Merck Sharp & Dohme was concerned that as far as possible the correct information was conveyed to the media and, therefore, it acted proactively. Merck Sharp & Dohme was acutely aware of the high degree of media interest in asthma generally and it was concerned that if the news management had been left to the media themselves, it was likely to be treated in a more superficial and inaccurate way which would have resulted in inappropriate messages to the general public.

The supplementary information to Clause 20.2 allowed for "... the provision of non-promotional information about prescription medicines to the general public ...".

That information must be "... factual and presented in a balanced way". Merck Sharp & Dohme believed the press material satisfied these requirements.

Clause 20.2 went on to state that "Statements must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine".

At no time in any of the interviews involving Dr Tomiak did he initiate or encourage any discussion about patients asking for Singulair from their doctor.

In response to a direct question from Peter Allen (Radio 5 Breakfast Programme), Dr Tomiak replied that an asthma patient should discuss with their doctor the "suitability" of this medication. This was a completely separate and distinct consideration from actually asking for the product to be prescribed to a patient. Indeed, there was no mention of the product by name (either branded or generic) in the course of the interview. Merck Sharp & Dohme asserted that this was not a breach of Clause 20.2. It felt it acted in an entirely reasonable and responsible way in answering this direct question.

Merck Sharp & Dohme reiterated its denial of any breach of the Code in any of its activities concerning Singulair and the media launch.

In considering the transcripts of the interviews that formed the subject matter of this complaint from Glaxo Wellcome, Merck Sharp & Dohme pointed out that it had had some difficulty in identifying the precise nature of Glaxo Wellcome's complaint. It had, therefore, assumed that the complaint referred to those parts of the transcript which had been annotated with an asterisk. Merck Sharp & Dohme dealt with them individually.

BBC Radio 5 - Breakfast Programme Report No: 0863/P98-020308

Report by Richard Hannaford, second paragraph:

"The National Asthma Campaign says people still need to keep their normal preventer inhalers, but in a few cases, the medicine could replace the current medication as a way of controlling their condition."

Merck Sharp & Dohme assumed the allegation was that this advice was outside the indications of Singulair.

Merck Sharp & Dohme stated that this was an opinion expressed by an independent third party and, therefore, outside the control of Merck Sharp & Dohme. The National Asthma Council's press release and facsimile from Merck Sharp & Dohme correcting the factual error were provided.

BBC Radio 5 - Breakfast Programme Report No: 0863/P98-020309

Dr Tomiak, page 4, second paragraph:

"Well the ... the medicine, of course, has to be reviewed by the licensing authorities, and it's been reviewed favourable [sic] by ... by the National Asthma Training Centre, who regard it as being an important advance."

Merck Sharp & Dohme asserted that both statements were statements of fact and entirely justified in the context of the interview. The first one was a statement of fact, the second an expression of opinion by an independent third party offered in good faith.

PANEL RULING

The Panel noted that complaints about items in the media were judged on the information provided by the pharmaceutical company or its agent to the journalists. When interviews with company representatives were reported a judgement would be made on what the representative said.

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, may 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 examined the media information pack which consisted of a folder containing three documents and the summary of product characteristics (SPC) for Singulair. The first document, a press release for consumer media/regional which was headed "First new class of anti-asthma drug for over two decades helps to reduce asthma attacks for adults and children", announced the launch of Singulair, discussed its indications and stated that studies had confirmed the benefits of use. The second and third documents provided background information for consumer/regional use. The second document, headed "Seven key facts, Singulair and Asthma" listed seven bullet points about the product and facts and figures about the UK asthma market. The third document, headed "Singulair and Asthma", discussed the pathology of the disease, types of treatment, how montelukast worked and its method of administration.

The Panel noted that the media information pack included an SPC for Singulair. The indication for the product was as add-on therapy in those patients with mild to moderate persistent asthma who were inadequately controlled on inhaled corticosteroids and in whom "as needed" short acting beta-agonists provided inadequate control. The Panel noted that the third document stated that montelukast could be prescribed for adults and children (aged six and over) with mild to moderate asthma when their symptoms were not well controlled by commonly used preventer and reliever treatments. The document stated that patients prescribed montelukast would carry on taking their usual preventer and reliever medicines. The other two documents stated that montelukast was add-on therapy but did not explain the need for patients to continue taking their usual preventers and relievers. In the Panel's view it might have been helpful to give more explicit details about the indication for Singulair than had been given in the press release and in the "Seven key facts" document.

The Panel examined the video news reel which began with a statement that montelukast was a new medicine and that patients prescribed the medicine would continue to take their usual inhalers. There was then a brief

overview of asthma followed by a series of interviews with a consultant chest physician, two general practitioners and two patients. The health professionals discussed the role of montelukast in the management of asthma while the patients described the impact that asthma had on their lives. There was also a sequence where a nurse measured a patient's peak flow.

The Panel noted the letter dated 3 February 1998 from Merck Sharp & Dohme to the National Asthma Campaign which corrected statements in its proposed press release to ensure it reflected Singulair's licensed use as an add-on therapy in patients inadequately controlled on normal preventer therapy rather than as first-line treatment.

The Panel did not accept that either the media information pack or the video news reel provided by Merck Sharp & Dohme constituted an advertisement for a prescription-only medicine to the general public. The Panel therefore ruled no breach of Clause 20.1 of the Code.

The Panel noted the requirements of Clause 20.2 of the Code. In the Panel's view the media information was not unreasonable in relation to the requirements of that clause. The Panel therefore ruled no breach of Clause 20.2 of the Code.

The Panel examined the transcript of the interview with Dr Richard Tomiak, Merck Sharp & Dohme's Director of Medical Affairs. The introduction to the interview referred to "A new pill". In the Panel's view listeners would know that they were about to hear about one specific medicine and not asthma therapy in general. The Panel noted that when asked whether most asthma sufferers would be able to go to a doctor and ask to try the new medicine, Dr Tomiak replied stating "Yes, I mean the ... asthma sufferers should go to their doctor and ask them if they are suitable for this medication. Obviously it won't be suitable for all patients but for the vast majority it may be suitable to control those patients who aren't controlled on their current treatments". In the opinion of the Panel this statement would encourage members of the public to ask their doctors to prescribe a specific medicine. The Panel noted that neither the medicine nor the company were mentioned by name during this interview but sufficient information had been provided to enable the medicine to be identified as Singulair. The Panel therefore ruled a breach of Clause 20.2 of the Code.

The Panel considered that the circumstances did not amount to a breach of Clause 2 of the Code and ruled no breach of that clause.

Complaint received **13 February 1998**

Case completed **29 May 1998**

CONSULTANT PHYSICIAN v MERCK SHARP & DOHME

Launch of Singulair

A consultant physician complained about the manner in which Singulair (montelukast) had been launched by Merck Sharp & Dohme. The product information had arrived on his desk on Friday, 6 February, an hour after he had been approached by the local radio station for comment. They were aware of the launch through a press release received from Merck Sharp & Dohme. On 10 February national newspapers and local papers bore stories describing this medicine as the first new form of treatment for asthma within twenty years. The complainant could see little reason for Merck Sharp & Dohme having issued the press statement other than to try and influence the general public. Such a public launch would result in significant pressure on general practitioners to prescribe the medicine, perhaps in inappropriate patients.

The Panel noted that the Code required that the introduction of a new medicine should not be made known to the general public until reasonable steps had been taken to inform the medical and pharmaceutical professions of its availability. It was unfortunate that the complainant had been contacted by the radio station to discuss the product before he had received any information about it. Nevertheless, the Panel considered that by mailing health professionals on 2 February and embargoing the consumer media press release until 9 February, the company had taken reasonable steps to ensure that health professionals were given prior notice of the launch. No breach of the Code was ruled in that regard.

In relation to the general comments made by the complainant about press coverage, the Panel considered that, in the absence of any specific allegations, its ruling in Case AUTH/678/2/98 regarding Merck Sharp & Dohme's media information pack and video news reel would also apply here. In Case AUTH/678/2/98 the Panel had examined these items but had not considered that they amounted to advertising to the public or that the information provided was unreasonable. The Panel ruled that there had been no breach of the Code in relation to these materials.

A consultant physician complained about the public launch of montelukast (Singulair) by Merck Sharp & Dohme Limited.

COMPLAINT

The complainant had been very concerned by the manner in which the new anti leukotriene medicine montelukast had been launched by Merck Sharp & Dohme. He thought Merck Sharp & Dohme might have breached the regulations with regard to the advertising of medicines to the general public. The product information arrived on his desk late on Friday, 6 February, some hour after he had been approached by the local radio station to make comment on it. They were aware of the launch of this product through a press release which they had received from Merck Sharp & Dohme itself. On 10 February 1998, the national newspapers and local papers also bore stories describing this medicine as the first new form of treatment for asthma within twenty years. The complainant understood that Clause 20.2 of the Code stated that information given to the general public should be factual, balanced, and must not be made for the purpose of encouraging members of the public to ask their doctors to prescribe a specific medicine. The complainant could see little reason for Merck Sharp & Dohme having issued this press statement, other than to try and influence the general public. While this new medication was promising, and indeed the first of its class to be licensed for use in the UK, it was neither revolutionary nor recently discovered. Public interest from a scientific point of view must therefore be limited.

The complainant was particularly concerned that such a public launch would result in significant pressure on general practitioners to prescribe this medication, perhaps in inappropriate patients. If this should happen, it might well be that a potentially very useful medicine had its reputation tarnished and in the future people who might benefit from it would have been denied the chance.

No doubt any benefit the company might attain from its current market approach would already have occurred but, nonetheless, the complainant said that he would much appreciate the Authority's view on whether it had acted appropriately.

RESPONSE

Merck Sharp & Dohme said that health professionals were informed of the launch of Singulair by an extensive mailing programme on 2 February 1998. As would be seen from the press material, which was provided, this news item was embargoed until Monday, 9 February. It was unfortunate if this particular radio station ignored the embargo but Merck Sharp & Dohme would state that the deliberate staggering of information was precisely intended to prevent a breach of Clause 20.4. Merck Sharp & Dohme submitted that it had taken all responsible steps within its control to prevent this and therefore denied the breach.

Merck Sharp & Dohme noted the physician's comments that in his opinion "Public interest from a scientific point of view must therefore be limited". In Merck Sharp & Dohme's opinion, the first new class of therapy in the treatment of asthma for over 20 years did constitute genuine news, and perhaps this was supported by the large coverage it received. Merck Sharp & Dohme contended that the press release was fully in compliance with Clause 20.2 in that it was factual and presented in a balanced way.

Contrary to the physician's assertion that the coverage would result in incorrect use of Singulair in "inappropriate patients", Merck Sharp & Dohme had emphasised in all its materials that it was add-on therapy for mild to moderate chronic asthmatics, not adequately controlled on "commonly used preventer and reliever treatments". Indeed, Merck Sharp & Dohme believed it important to issue a press release in order to ensure, in so far as possible, that the information received by the public was balanced and accurate.

Given the potential news value of this medicine, Merck Sharp & Dohme was concerned that as far as possible the correct information was conveyed to the media. It strongly refuted any suggestion that it had breached Clause 20.2 of 20.4 in any way.

PANEL RULING

The Panel noted the requirements of Clause 20.4 of the Code that the introduction of a new medicine must not be made known to the general public until reasonable steps had been taken to inform the medical and pharmaceutical professions of its availability. The Panel noted that health professionals were notified of the product launch by a mailing on 2 February.

The Panel noted that the complainant had been contacted by a local radio station to discuss the medicine on 6 February. The Panel examined the press pack and noted that the document headed "Press release - Consumer Media/Regional" stated in bold type, that the item was embargoed for use until 00.01 GMT hours on Monday 9 February. It was unfortunate that the radio station had contacted the complainant to discuss the product before the complainant had received any information on it. Nevertheless the Panel considered that the company by mailing health professionals on 2 February and embargoing the consumer media press release until 9 February had taken reasonable steps to ensure that health professionals were given prior notification of the launch. The Panel therefore ruled no breach of Clause 20.4.

The Panel noted the complainant had made general comments about the press coverage. The Panel considered that in the absence of any specific allegations its rulings in Case AUTH/678/2/98 regarding the media information pack and video news reel provided by Merck Sharp & Dohme would also apply here. The Panel's rulings were as follows:

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, may 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 examined the media information pack which consisted of a folder containing three documents and the summary of product characteristics (SPC) for Singulair. The first document, a press release for consumer media/regional which was headed "First new class of anti-asthma drug for over two decades helps to reduce asthma attacks for adults and children" announced the launch of Singulair, discussed its indications and stated that studies had confirmed the benefits of use. A second and third document provided background information for consumer/regional use. The second document, headed "Seven key facts, Singulair and Asthma" listed seven bullet points about the product and facts and figures about the UK asthma market. The third document, headed "Singulair and Asthma" discussed the pathology of the disease, types of treatment, how montelukast worked and its method of administration.

The Panel noted that the media information pack included an SPC for Singulair. The indication for the product was as add-on therapy in those patients with mild to moderate persistent asthma who were inadequately controlled on inhaled corticosteroids and in whom "as needed" short acting beta-agonists provided inadequate control. The Panel noted that the third document stated that montelukast could be prescribed for adults and children (aged six and over) with mild to moderate asthma when their symptoms were not well controlled by commonly used preventer and reliever treatments. The document stated that patients prescribed montelukast would carry on taken their usual preventer and reliever medicines. The other two documents stated that montelukast was add-on therapy but did not explain the need for patients to continue taking their usual preventers and relievers. In the Panel's view it might have been helpful to give more explicit details about the indication for Singulair than had been given in the press release and in the "Seven key facts" document.

The Panel examined the video news reel which began with a statement that montelukast was a new medicine and that patients prescribed the medicine would continue to take their usual inhalers. There was then a brief overview of asthma followed by a series of interviews with a consultant chest physician, two general practitioners and two patients. The health professionals discussed the role of montelukast in the management of asthma while the patients described the impact that asthma had on their lives. There was also a sequence where a nurse measured a patient's peak flow.

The Panel did not accept that either the media information pack or the Video News Reel provided by Merck Sharp & Dohme constituted an advertisement for a prescription-only medicine to the general public. The Panel therefore ruled no breach of Clause 20.1 of the Code.

The Panel noted the requirements of Clause 20.2 of the Code. In the Panel's view the media information was not unreasonable in relation to the requirements of that clause. The Panel therefore ruled no breach of Clause 20.2 of the Code.

Complaint received **13 February 1998**

Case completed **1 June 1998**

GENERAL PRACTITIONER v BRISTOL-MYERS SQUIBB AND SANOFI WINTHROP

Aprovel leavepiece

A general practitioner complained about a photograph on the front cover of an Aprovel leavepiece issued by Bristol-Myers Squibb and Sanofi Winthrop. The photograph depicted a woman standing on a swing kissing a man who was suspended upside down from the top of the swing. Above the photograph was the caption "Aprovel is what you get when you get it right".

The complainant said that Aprovel was being marketed for those patients, especially male patients, who were getting unacceptable side effects, including sexual dysfunction, from their previous medication. The complainant objected to the photograph, the implication of which was that the man, who looked about 35, was not getting any sexual dysfunction and was feeling very well. Unfortunately the girl who was kissing him looked about 14 or 15. The representative who had given him the leavepiece had said that the girl was only 14 years old. As the product was being sold on the fact that it had less side effects, including sexual dysfunction, it was completely inappropriate and in bad taste that the company showed a 35 year old man kissing a 14 year old girl. The implication was that if the man was on the product then the relationship might go on to a sexual one.

The Panel did not accept that the woman appeared to be 14 or 15 years old. The Panel considered that the woman, although still young, appeared to be older and more mature than that. The model who had posed for the photograph was in fact 26 years old. The Panel did not consider that the photograph suggested any impropriety with respect to the ages of the man and the woman or that, in terms of their relative ages, it was likely to offend the audience to which it was targeted. It was ruled that there had been no breach of the Code.

A general practitioner submitted a complaint about a photograph featured on the front of an Aprovel leavepiece (APR/0897/041) issued by Bristol-Myers Squibb Pharmaceuticals Limited and Sanofi Winthrop Limited. The photograph depicted a swing. A woman stood on the seat of the swing kissing a man who was suspended upside down from the top of the swing. Above the photograph was the caption "Aprovel is what you get when you get it right".

COMPLAINT

The complainant stated that Aprovel, because it had a low side effect profile in line with placebo, was being marketed as a third line medicine for those patients, especially male patients, who were getting unacceptable side effects from their previous medication. Some of this was obvious sexual dysfunction and the claim was that this product had the same level of side effects as placebo. The complainant did not doubt that, but it was claiming that it had a lower side effect profile with sexual dysfunction, hence the advertisement. The part of the leavepiece the complainant objected to was the front showing a loop chain with a man hanging from it upside down kissing a woman at the bottom of the chain. The implication was that the gentleman, who looked about 35, was not getting any sexual dysfunction and was feeling very well. Unfortunately the girl who was kissing him looked about 14 or 15. The complainant stated that he had been told by the company representative who gave him the literature that the model was only 14 years old. The complainant submitted that as this product was being sold on the fact that it had less side effects, including sexual side effects, it was completely inappropriate and in bad taste that the company showed the 35 year old man kissing a 14 year old girl. The implication was that if the man in the advertisement was on this product then the relationship might go on to a sexual one. As the girl looked and was under age, the complainant thought this was inappropriate and stated that the company should have used a 30 year old woman at the lower end.

The complainant stated that he would like the company to withdraw the advertisement in its present form as the implication was that its product either made male patients into paedophiles or made them extremely attractive to under age girls.

RESPONSE

Bristol-Myers Squibb and Sanofi Winthrop submitted a joint response.

The companies confirmed that the leavepiece was provided by representatives to doctors after discussing the product. They addressed the doctor's complaint point by point.

1 Aprovel was marketed as a third line anti-hypertensive medicine for those patients, especially male patients, who were getting unacceptable side effects from their previous medication.

Aprovel was licensed for the treatment of hypertension for both male and female patients. It was neither solely licensed nor being marketed as a third line treatment for hypertension in patients with side effects from their previous medications, and nowhere in the promotional material was there a distinction made between its use in male and female patients.

2 It was claiming that it had a lower side effect profile with sexual dysfunction, hence the advertisement.

Bristol-Myers Squibb and Sanofi Winthrop stated that in placebo controlled trials Aprovel demonstrated a tolerability profile which was similar to placebo. Data from these studies showed that sexual dysfunction was one of many adverse events reported by patients who received either Aprovel or placebo. The percentage of patients who reported sexual dysfunction was small (<1%, n=2,606) and not statistically significantly different

between the two groups. The graph on page three of the leavepiece did not unduly emphasise sexual dysfunction as an adverse event in comparison with the other events such as headache, dizziness, fatigue, oedema and cough. The bar chart did not imply that the frequency of sexual dysfunction was less with Aprovel than with placebo.

Bristol-Myers Squibb and Sanofi Winthrop pointed out that nowhere in the leavepiece was it claimed that Aprovel had a "lower" side effect profile of sexual dysfunction.

3 **The implication was that the gentleman, who looked about 35, was not getting any sexual dysfunction and was feeling very well. Unfortunately the girl at the bottom of the chain who was kissing him looked about 14 or 15. I was told by the company representative who gave me the literature that she was only 14 years old.**

Bristol-Myers Squibb and Sanofi Winthrop stated that the advertisement showed the back of a man and woman, with the man hanging upside down on a swing and being kissed by a woman. They were both fully clothed in plain black and white outfits. The woman used in the advertisement was a professional model and was 26 years old. The allegation that an under age girl of 14 years old was used for the photoshoot was therefore untrue.

Company representatives had not been advised of the age of the woman in the advertisement and would have no reason to comment on the age of the model. Bristol-Myers Squibb and Sanofi Winthrop stated that obviously without further information regarding the identity of the representative they could not investigate the allegation regarding the statement which in itself was false.

4 **It was completely inappropriate and in bad taste that the company showed the 35 year old man kissing a 14 year old girl. The implication was that if the man was on the product then the relationship might go on to a sexual one. I would like the company to withdraw the advertisement in its present form as the implication is that its product either made male patients into paedophiles or made them extremely attractive to under age girls.**

Bristol-Myers Squibb and Sanofi Winthrop submitted that there was no implication from the advertisement that if the man was on Aprovel the relationship would become a sexual one. The girl was not 14 years old, she was 26 years old.

Bristol-Myers Squibb and Sanofi Winthrop stated that they had not received any other complaints about the advertisement being in bad taste. While they accepted that taste was subjective, they would contend that this advertisement was not offensive on grounds of taste.

The advertisement was tested in doctors' focus groups before it was launched. Data from the market research indicated that the advertisement was well liked and enjoyed by the doctors. In general, it conveyed a positive image and none of them considered that it was in bad taste. None of the doctors indicated that the advertisement implied sexual impropriety. The pose of the couple on the swing was not portrayed as sexual or contrived but it presented the 'approval' idea in an attractive and unusual way.

The advertisement in its present form did not, nor was it intended, to imply that Aprovel made male patients into paedophiles or made them extremely attractive to under age girls.

PANEL RULING

The Panel noted that the supplementary information to Clause 9.1 of the Code stated that the special nature of medicines and the professional audience to which the material was directed required that the standards set for the promotion of medicines were higher than those which might be acceptable for general commodity advertising. It was unacceptable to use sexual imagery for the purpose of attracting attention to the promotional material.

While it was difficult to determine the age of either the man or the woman in the photograph, the Panel did not accept that the woman appeared to be 14 or 15 years old. The Panel considered that the woman, although still young, appeared to be older and more mature than that. The Panel noted that the model who posed for the photograph was in fact 26 years old. The Panel did not consider that the photograph suggested any impropriety with respect to the age of the man and the woman or that, in terms of their relative ages, it was likely to offend the audience to whom it was targeted. No breach of Clause 9.1 was ruled.

Complaint received **24 February 1998**

Case completed **12 May 1998**

CASE AUTH/686/3/98

LOCAL RESEARCH ETHICS COMMITTEE v PHARMACIA & UPJOHN

Focus Group meeting

A local research ethics committee complained about a letter which a member of the committee had received from Pharmacia & Upjohn. The letter was an invitation to attend an evening meeting to be held in a hotel entitled "Focus Group - The Introduction to General Practice of the Concept of Improved Social Functioning linked to a selective Noradrenaline re-uptake inhibitor". The meeting was to involve about ten clinicians to discuss the likely future development of antidepressants from a marketing perspective. The committee had expressed concern as to whether the approach breached the Code. Comment would be welcomed particularly in relation to the statement that "We hope that you will be able to participate. An honorarium of £200 will be payable and travel costs will be reimbursed".

The Panel considered that it was not unacceptable for companies to pay healthcare professionals and others for advice as to how products should be promoted. It was a question of deciding where the boundary lay. There had been a previous case involving a focus group meeting held by Pharmacia & Upjohn (Case AUTH/471/10/96). Although the Panel had had some concerns about that meeting, it had ruled there not to have been a breach. In that case there had just one such meeting whereas ten had been held in various locations in the present case. The Panel was concerned about the number of meetings and considered that Pharmacia & Upjohn had not given sufficient justification regarding regional variations in the management of depression to justify the number of meetings held. The Panel considered that the meetings constituted a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings and a breach of the Code was ruled.

Upon appeal by Pharmacia & Upjohn, the Appeal Board considered that as a principle it was acceptable for companies to pay healthcare professionals and others for advice as to how their products should be promoted. The Appeal Board noted that Pharmacia & Upjohn had written to 41 psychiatrists in south west England. The invitation stated that places were limited and would be allocated on a first come first served basis. The Appeal Board considered there was a difference between inviting a small number of specific doctors, eg opinion leaders, to inviting a relatively large number of doctors on a first come first served basis. In the Appeal Board's view there had not been sufficient targeting of the invitation. The Appeal Board was concerned at the number of meetings.

The Appeal Board considered that although the concept was acceptable, the arrangements for the meetings in question meant that they constituted a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings. The Appeal Board upheld the Panel's ruling of a breach of the Code.

A local research ethics committee complained about a letter which a member of the committee had received from Pharmacia & Upjohn Limited. The letter was an invitation to attend a meeting to be held in a hotel and was entitled "Focus Group - The Introduction to General Practice of the Concept of Improved Social Functioning, linked to a selective Noradrenaline re-uptake inhibitor". The meeting was to involve about ten clinicians to discuss the likely future development of antidepressants from a marketing perspective. The stated purpose was "... to obtain a perspective on the current management of depression and to establish a platform for the introduction of a highly selective Noradrenaline Reuptake Inhibitor to the Primary Care Health Sector in the UK". The meeting was to start with coffee and drinks at 6pm. A working dinner was to be provided at 8pm. There would be a 45 minute presentation on "Social Functioning and the Role of Noradrenaline" and a 30 minute presentation on "The Market, and Proposed Approach". Most of the remaining time was to be devoted to an interactive marketing workshop.

COMPLAINT

Concern had been expressed at a meeting of the committee as to whether the approach breached the Code. Comments upon it would be welcomed, particularly in relation to the penultimate paragraph of the letter of invitation which read: "We hope that you will be able to participate. An honorarium of £200 will be payable and travel costs will be reimbursed." Comment was also requested as to whether the fact that the approach had been to a member of a local research ethics committee made the approach unethical.

RESPONSE

Pharmacia & Upjohn said that an invitation was extended, in writing, to 41 psychiatrists to attend an interactive workshop to explore various issues related to the management of depression and in particular to discuss the importance of social functioning in depression together with the role of noradrenaline, both in the aetiology and pharmacotherapy of depression. The psychiatrists had been identified because of their clinical experience in treating depression and location in the south west of England and not because of their affiliation with any organisation. In fact Pharmacia & Upjohn was unaware of additional responsibilities of any invitees. The fact that an invitation was sent to a doctor who was a local research ethics committee member did not impact on the ethics or the professional standards of the meeting.

The intended role of all the psychiatrists was to act as consultants to Pharmacia & Upjohn in order to advise the company of the marketing relevance of these issues within their locality. Therefore the nature of the workshop was arranged such that all the psychiatrists were actively involved all the way through the meeting.

Seven consultant psychiatrists attended this focus group on 19 February 1998. They were joined by three members of the marketing team as well as by an external consultant. After a welcome and introduction from the marketing director of the company, the consultant gave a 45 minute presentation on various issues relating to

depression including the role of noradrenaline in depression (both in its aetiology and treatment), clinical data comparing a noradrenergic antidepressant with selective serotonin reuptake inhibitors and tricyclic antidepressants, and the importance and measurement of social functioning in depression. The latter section involved exploring the merits of a recently developed scale to measure social functioning. The group was then given a 30 minute presentation on the antidepressant market and current strategies for marketing antidepressants.

These two presentations provided the necessary platform for the group to discuss the issues outlined above and not surprisingly there was plenty of discussion between the focus group and the two presenters. A modest buffet dinner was provided which was taken during the group work.

For the remainder of the meeting (approximately two hours) the focus group discussed the following issues:

1 The aims of therapy in depressive illness.

2 The importance of social functioning in depression and the merits of a new tool to measure social functioning, the social adaptation self-evaluation questionnaire.

3 The advantages of clinician rated and patient rated assessments in evaluating response to antidepressant treatment.

4 Experience with noradrenergic antidepressants in the treatment of depression.

The group presented its findings and again at this point there was considerable discussion.

The layout of the meeting was such that each attendee had to participate. The meeting lasted approximately three and a half hours and the majority of the meeting was clearly of a scientific and interactive nature. The honorarium of £200 in total was modest (and less than BMA Fees Guideline Schedule: The fee payable for participation in clinical trials was £121 per hour). Pharmacia & Upjohn therefore did not consider that Clauses 18.1 or 19.1 of the Code were breached.

Pharmacia & Upjohn stressed that no promotional literature, exhibition materials or branding items were present on the site, either within the room or outside. Neither was any additional material given to the group. No sales representatives were present. The dates and locations of nine other similar focus group meetings which had been held nationally were provided. No further meetings on this particular subject were planned.

PANEL RULING

The Panel accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company. The Panel noted that there had been a previous case involving a focus group meeting held by Pharmacia & Upjohn (Case AUTH/471/10/96). On that occasion the Panel had had some concerns about the meeting. The Panel noted that those attending the meeting had been invited to act as consultants to the company. The number of delegates had been limited thus ensuring that all could make a contribution to the proceedings. On balance an honorarium of £200 had not been unreasonable for the amount of work involved. The hospitality had been acceptable. No breach of the Code was ruled. The Panel noted that there were differences between the previous case and the one now before it (Case AUTH/686/3/98).

In the case now before it the Panel noted that the purpose of the focus group meeting was to "... obtain a perspective on the current management of depression and to establish a platform for the introduction of a highly selective Noradrenaline Reuptake Inhibitor to the Primary Care Health Sector in the UK". One of the presentations was entitled "Social functioning and the role of Noradrenaline". The Panel noted that Pharmacia & Upjohn's product Edronax was a selective noradrenaline reuptake inhibitor.

The Panel noted that ten such focus group meetings had been held, not just one only, as in Case AUTH/471/10/96. The meetings had been held between September 1997 and February 1998 at various locations around the UK. The company had invited in writing 41 consultants to attend the meeting in question. The invitation stated that the workshop would involve about ten clinicians. The invitation stated that "there will be the possibility of discussing relevant local issues which may have been identified during our discussion". Seven consultants had in fact attended the meeting. Given the number of delegates who had attended the meeting on 19 February 1998, the Panel calculated that overall approximately 70 delegates would have attended the ten meetings. In the Panel's view it was questionable whether all the psychiatrists would have truly acted as consultants to the company, each giving such advice as to justify a £200 honorarium and reimbursement of travel expenses.

The Panel considered that it was not unacceptable for companies to pay healthcare professionals and others for advice as to how products should be promoted. It was a question of deciding where the boundary lay. The Panel noted that it appeared that the arrangements for each focus group meeting were almost identical to the meeting considered in Case AUTH/471/10/96. The Panel was concerned about the number of meetings.

It considered that Pharmacia & Upjohn had not given sufficient justification regarding regional variations in the management of depression to support the number of meetings held. The Panel considered that the ten meetings constituted a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings. The Panel considered that the only relevant clause in the Code was Clause 18.1. The Panel therefore ruled a breach of Clause 18.1.

The Panel did not consider that the fact that one of those approached was a member of a local research ethics committee was a relevant factor in the matter.

APPEAL BY PHARMACIA & UPJOHN

Pharmacia & Upjohn submitted that it was very difficult to reconcile the Panel's ruling of a breach of Clause 18.1 of the Code with the Panel's ruling in the previous case, AUTH/471/10/96, which concluded that an honorarium of £200 for such a meeting was acceptable. The Edronax meetings were structured in exactly the same way and the

payment was also the same. The company therefore entered into this consultative programme confident that this approach had the Authority's approval.

With regard to the Panel's view that the company had not given sufficient justification regarding regional variations in the management of depression to support the number of meetings, it was unable to find any reference in the Code to the number of meetings having an impact on the acceptability of the remuneration for a given amount of work. As a proportion of prescribing psychiatrists (there were currently over 7000 members of the Royal College of Psychiatrists) the company deemed the sample consulted to be small but hopefully representative. The total number of meetings was misleading because the Edronax summary of product characteristics was changed on 5 October following the mutual recognition process in the EU. The changes were by no means minor and included loss of the indication "for use in the elderly", as well as numerous additions for the sections covering "contra-indications", "special warnings and precautions for use" and "interactions". This invalidated much of the work carried out in September and made it necessary for the company to reconsult. The company emphasised that at no point did it consider that this might have an impact on the way in which the Code could be interpreted.

In summary, the company submitted that the Panel's ruling on this occasion was inconsistent with that in 1996 and it did not consider that either the spirit or the letter of Clause 18.1 had been breached.

APPEAL BOARD RULING

The Appeal Board considered that as a principle it was acceptable for companies to pay healthcare professionals and others for advice as to how their products should be promoted. The arrangements needed to comply with the Code.

The Appeal Board noted that Pharmacia & Upjohn had written to 41 psychiatrists in south west England. The invitation stated that places were limited and would be allocated on a first come first served basis. The Appeal Board considered there was a difference between inviting a small number of specific doctors, eg opinion leaders, to inviting a relatively large number of doctors on a first come first served basis. In the Appeal Board's view there had not been sufficient targeting of the invitation. The Appeal Board was concerned at the number of meetings.

The Appeal Board considered that although the concept was acceptable, the arrangements for the meetings in question meant that they constituted a series of promotional meetings. It was not appropriate to pay doctors to attend such meetings. The Appeal Board upheld the Panel's ruling of a breach of Clause 18.1 of the Code.

The appeal therefore failed.

Complaint received **6 March 1998**

Case completed **2 July 1998**

CASE AUTH/689/3/98

ASTRA v WYETH

Financial support for audit

Astra complained about financial support provided to a health authority by Wyeth so that practices could carry out a proton pump inhibitor audit on their patients with a view to reducing prescribing costs by switching them from omeprazole (Astra's Losec) to lansoprazole (Wyeth's Zoton). It was alleged that this was an inducement to prescribe in breach of the Code.

The Panel noted that, in essence, Wyeth was providing grants to pay the costs incurred by general practices in reviewing their patients and deciding which of them to switch from omeprazole to lansoprazole. It seemed to the Panel that, while it might be argued that this amounted to the provision of a service which would enhance patient care or benefit the National Health Service, as referred to in the supplementary information to the Code, the real purpose, and certainly the effect, of the sponsorship was to boost the prescribing of lansoprazole at the expense of that of omeprazole. The Panel considered that funding for this purpose was unacceptable and ruled it in breach of the Code.

COMPLAINT

Astra Pharmaceuticals Ltd complained about the activities of Wyeth in providing financial support for a proton pump inhibitor audit implemented by a health authority which Astra alleged contravened Clause 18.1 of the Code of Practice.

Astra drew attention to the health authority's information bulletin which stated that, in its opinion, "for its licensed indications, the PPI of choice must be lansoprazole" and went on to state that practices wishing to switch from omeprazole to lansoprazole might apply to the health authority for support to help them with this switch. Omeprazole was Astra's product Losec and lansoprazole was Wyeth's product Zoton.

Astra also referred to a letter on proton pump inhibitor audit which accompanied the bulletin. The letter stated that reimbursement of costs was available to practices to perform a review and make the switch, through support from Wyeth Laboratories.

In Astra's view the work involved for the practice staff to conduct such a review was considerable and therefore motivation to do this was likely to be facilitated by the offer of reimbursement of costs.

Wyeth had told Astra that an audit grant was provided to the health authority for the review of patients on long term GI medication. However, the letter from the health authority stated that Wyeth Laboratories had provided

support for practices wishing to perform the review and make the switch. A general review of patients on long term GI medication was very different from a practice review and specific switching from one proton pump inhibitor to another.

This raised several questions about the provision of this grant:

1 Were discussions re the provision of this grant initiated by the health authority or Wyeth?

2 Was Wyeth aware that the grant was to be used to support a practice review and switch and did it influence this in any way?

3 If financial support had not been provided by Wyeth, would the practice review and switch have gone ahead?

Astra was concerned by the linkage between financial support from Wyeth and the switch from omeprazole to lansoprazole in general practices under the health authority. This type of financial linkage did not, in Astra's view, constitute acceptable industry practice and Astra alleged that it represented an inducement to prescribe in contravention of Clause 18.1 of the Code.

RESPONSE

Wyeth rejected Astra's assertion that the assistance it had provided to the health authority in relation to its proton pump inhibitor audit contravened Clause 18.1. or indeed any other provision of the Code.

1 How the arrangement came about

The health authority had long had a policy to explore the potential benefits of a closer working relationship with the pharmaceutical industry generally. To this end, it had in recent years discussed with Wyeth and a number of other companies areas in which co-operation could be appropriate. In March 1997, the health authority invited representatives from a number of pharmaceutical companies to a meeting with its chief executive, director of primary care and a number of its medical and pharmaceutical advisers. The purpose of the meeting was to explore in greater depth the possibilities for co-operation and, as a result, the medical adviser was given the lead to develop relationships specifically relating to prescribing issues.

Facilitating a change in prescribing from one medication to another on the basis of sound evidence-based criteria was standard practice among prudent health service managers. As a result of further discussions with Wyeth, the health authority formed the view in relation to proton pump inhibitors (PPIs) that, given that there were no material differences between lansoprazole and omeprazole in terms of efficacy and safety, it was appropriate to factor cost into the decision to prescribe. The health authority noted that the price of lansoprazole at that time was approximately 20% below that for omeprazole. Accordingly, the health authority decided to act to facilitate amongst its GP practices a switch in prescribing from omeprazole to lansoprazole wherever appropriate and asked for Wyeth's financial assistance in support of the additional administrative costs of the patient audit and review which this initiative would require as these costs would fall outside the scope of GMS reimbursement provisions.

2 Full details of the arrangement

a) Using PACT data, the health authority identified practices which were high users of proton pump inhibitors. The health authority then drew up a cost savings analysis for each of the subject practices, based on a change in prescribing from omeprazole to lansoprazole;

b) Medical and pharmaceutical advisers then visited the practices and, with the cost savings analyses, discussed the relative merits of lansoprazole and omeprazole. The practice was made aware that the cost of making the change (ie cost of identifying patients, GP review and implementation where appropriate) would be reimbursed by the health authority out of monies made available by Wyeth;

c) Practices which decided to make the change in appropriate cases notified the health authority in writing to this effect. The reimbursement payment was "triggered" by a switch from omeprazole to lansoprazole in at least 80% of those patients identified for audit. The health authority took the view that 20% was a sufficient margin to accommodate prescribers' clinical freedom and any patient preferences; and

d) Thereafter, the practices' use of proton pump inhibitors was monitored through PACT data.

3 Amount of financial assistance

Although there were 90 practices within the Authority's area, it was agreed that Wyeth would provide immediate funding for audit of 30 practices only. No staff, facilities, or other forms of support were provided. The manner and extent of Wyeth's support was determined solely by the health authority. The health authority had given Wyeth the option to provide further funding on the same basis if the audit was extended beyond the original 30 practices.

Summary

In identifying and acting upon the cost differential between lansoprazole and omeprazole, the health authority had done what all institutions within the NHS sought to do, namely provide the best patient care at the lowest cost to the tax payer. The complainant was of course free to question the basis upon which the health authority had initiated this review but, given the modest sums available for reimbursement, it was in Wyeth's view quite clear that the motivation for the change in prescribing came not from the availability of reimbursement but from the significant cost savings resulting from the change.

Accordingly, Wyeth's role had been limited to the provision of very modest sums to assist with the administrative support of an initiative which would significantly benefit the NHS and was, in Wyeth's submission, entirely consistent with the supplementary information relating to the provision of medical and educational goods and services which appeared alongside Clause 18.1 of the Code.

The health authority had approved Wyeth's letter of response and had indicated that it fully endorsed the content of it.

PANEL RULING

The Panel noted that the health authority letter stated that in order to support practices wishing to perform the review and make the switch the health authority (through support from Wyeth) was willing to reimburse practices for the administrative staff time to search patient notes etc, printing or postage costs incurred in writing to patients and one or two half day locum sessions to allow GPs to review notes or plan the practice's approach to the change. Reimbursement would be made on completion of the switch.

The Panel noted that, in essence, Wyeth was providing grants to pay the costs incurred by general practices in reviewing their patients and deciding which of them to switch from omeprazole to lansoprazole. The Panel noted Wyeth's submission that the reimbursement payment was triggered by a switch from omeprazole to lansoprazole in at least 80% of those patients identified for audit. It seemed to the Panel that, while it might be argued that this amounted to the provision of a service which would enhance patient care or benefit the National Health Service, as referred to in the supplementary information to Clause 18.1 of the Code, the real purpose, and certainly the effect, of the sponsorship was to boost the prescribing of lansoprazole at the expense of that of omeprazole. The Panel considered that funding for this purpose was unacceptable and ruled a breach of Clause 18.1 of the Code.

Complaint received 26 March 1998

Case completed 9 June 1998

CASE AUTH/690/3/98 *NO BREACH OF THE CODE*

HOSPITAL PHARMACIST v SMITHKLINE BEECHAM

Kytril Mailing

A hospital pharmacist concerned with cancer services complained about a mailing for Kytril issued by SmithKline Beecham, alleging that it trivialised chemotherapy induced vomiting and was in poor taste. The single page card bore an illustration of a matron and a patient which appeared to have been taken from a "Carry On" film. The text stated that Kytril was "A SmithKline Beecham Oncology Release" and that it had been nominated for 50 Oscars, 14 Malcolms, 250 Peters, 13 Janes and thousands of others.

The Panel accepted that the humourous style adopted in the mailing would offend some of the recipients but did not consider that the majority would find it objectionable. Matters of taste were subjective and tastes would differ. The Panel ruled that there had been no breach of the Code in this regard.

A hospital pharmacist concerned with cancer services complained about a single page, A5 mailing for Kytril issued by SmithKline Beecham Oncology. It was headed "Carry on 'Kytril'" and bore an illustration of a matron and a patient which appeared to have been taken from a "Carry On" film. The text stated that Kytril was "A SmithKline Beecham Oncology Release" and that it had been nominated for 50 Oscars, 14 Malcolms, 250 Peters, 13 Janes and thousands of others. There was no prescribing information and the generic name was not given. The reverse of the mailing indicated that the mailing was copyright 1998 SmithKline Beecham.

COMPLAINT

The complainant alleged that the mailing trivialised chemotherapy induced nausea and vomiting and was in poor taste.

RESPONSE

SmithKline Beecham Pharmaceuticals UK said that the mailing had been sent to those customers dealing with chemotherapy and cancer patients on a regular basis and with whom SmithKline Beecham had developed a working relationship.

During the recent discussions about a potential merger between SmithKline Beecham and Glaxo Wellcome, the commonest question SmithKline Beecham had been asked by those customers was what was happening with Kytril, and this mailing followed on from the breakdown of merger discussions and was sent as a light-hearted way of reassuring customers that Kytril would remain available. Although the approach was light-hearted, it was certainly not SmithKline Beecham's intention that the treatment of chemotherapy induced nausea and vomiting or the distress that patients experienced was trivialised and the company did not believe that the majority of its customers would see it in that way.

The company believed that the mailing emphasised SmithKline Beecham Oncology's commitment to continuing to improve the quality of life of many thousands of cancer patients and in particular to the continuing availability of Kytril.

SmithKline Beecham did not believe that it was in breach of Clause 9.1 of the Code.

PANEL RULING

The Panel first considered whether the mailing came within the scope of the Code or whether it should be regarded as being excluded on the basis that it was a factual announcement which included no product claims, one of the exceptions to the Code provided for in Clause 1.2. The Panel decided that the exception did not apply in this instance because of the florid promotional style which had been adopted and because of the reference to oncology.

The Panel accepted that the humorous style adopted in the mailing would offend some of the recipients but did not consider that the majority would find it objectionable.

Matters of taste were, of course, subjective and attitudes would differ. The Panel ruled that there had been no breach of Clause 9.1 of the Code.

The Panel asked that SmithKline Beecham's attention be drawn to the fact that the mailing should have borne prescribing information as required by Clause 4.1 of the Code. The mailing should also have included the date, and not just the year, on which the mailing was drawn up or last revised as required by Clause 4.7 of the Code.

Complaint received **30 March 1998**

Case completed **2 June 1998**

CASE AUTH/691/4/98

PASTEUR MÉRIEUX MSD v WYETH

Inducement to purchase Begrivac

Pasteur Mérieux MSD said that in addition to large discounts on its influenza vaccine, Begrivac, Wyeth was offering practices which purchased it a sum of money to be used for training. The amount was calculated as a percentage of the value of the Begrivac order The arrangement could not be regarded as a package deal because the associated benefits were not relevant to the vaccine. It was further alleged that discredit was brought upon the industry because Wyeth was inducing buyers to cancel their existing orders and switch to Wyeth.

The Panel noted that it had recently ruled that if arrangements were to be seen as a package deal, as referred to in the supplementary information to the Code, then the associated benefits had to be relevant to the medicine or medicines purchased. Wyeth had acknowledged that that principle now made its arrangement unacceptable. The Panel considered that the training support offered was not relevant to the purchase of Begrivac and a breach of the Code was ruled. The Panel did not consider that discredit had been brought upon the industry by Wyeth's conduct and no breach was ruled in that regard.

COMPLAINT

Pasteur Mérieux MSD Ltd stated that the current terms of business for the sale of Wyeth's vaccine Begrivac, inactivated split virion influenza virus, included a clear inducement to purchase and prescribe and alleged that Wyeth was in breach of Clause 18.1 of the Code. In addition, Wyeth was using this inducement to encourage doctors and GP buying groups to break contracts with other influenza vaccine suppliers. This portrayed the pharmaceutical industry in a very poor light. As a result, it was alleged that Wyeth was also bringing discredit to, and reduction of confidence in, the industry, in breach of Clause 2 of the Code.

During January and February 1998, Pasteur Mérieux MSD received reports that, in addition to large discounts on its influenza vaccine Begrivac, Wyeth was offering practices a sum of money to be used for training. The amount available for training was calculated as a percentage of the value of the Begrivac order. Wyeth was presently offering 3% of the total order value.

A recent letter from the managing director of Wyeth to Pasteur Mérieux MSD stated "... our current terms of business for the sale of Begrivac to GP practices, which include an offer to Practice Training Support up to a percentage value of the total order value. The support can either be provided by or funded by Wyeth. Consequently, I can confirm that the benefit is directly related to sales.".

Pasteur Mérieux MSD said that the offer of practice training support was in breach of Clause 18.1 of the Code for the following reasons:

- Wyeth was offering a benefit in kind/pecuniary advantage to members of the health professions as an inducement to prescribe, supply, administer and buy Begrivac.
- If the practices did not order Begrivac, they did not benefit from the training on offer.
- The type of training to be provided was not specified, nor, as far as Pasteur Mérieux MSD was aware, was it subject to scrutiny, by Wyeth. As a result the offer was open to misinterpretation by health professionals. There were no safeguards to ensure that the money was not being used for personal benefit or indeed for something completely unrelated to the practice of medicine.
- The sum on offer was of significant value.
- The benefit was not justified by any of the criteria set out in the supplementary information to Clause 18.1.
- In the letter referred to above Wyeth stated "For a package deal to be acceptable, such a benefit has to be "fair and reasonable"; there is not, as you appear to imply, any requirement for it to relate directly to the medicinal product being sold.". This statement was clearly at odds with the judgement in Case AUTH/600/8/97 which stated "In the Panel's view, in order for arrangements to be seen as a package deal, the associated benefits had to be relevant to the medicine or medicines purchased.".

Pasteur Mérieux MSD alleged that the offer of practice training support was in breach of Clause 2 of the Code for the following reasons:

- Wyeth was approaching practices and buying groups which had already placed orders with other influenza vaccine suppliers.
- In addition to offering similar discounts to other suppliers Wyeth was offering practice training support as an incentive to the practices and buying groups to cancel their existing orders and to switch to Wyeth.

Pasteur Mérieux MSD was extremely concerned that this

"market stall" approach to business would bring discredit to, and reduction of confidence in, the industry. Pasteur Mérieux MSD alleged that this placed Wyeth in breach of Clause 2 of the Code.

RESPONSE

By way of background, Wyeth stated that the offer of practice training support was introduced in early 1997 as part of a package deal to GP practices purchasing Wyeth's vaccines. Training support was offered up to a maximum percentage of the practice's order at list prices. Wyeth's terms did not require the training to be directly related to its influenza vaccine, Begrivac, provided that it was relevant to the practice of medicine. The training might be provided by Wyeth or funded by Wyeth, either by paying for external course providers or paying the practice to organise such training. In the latter case, documented costs information was requested before such funding was given. As an indication of the relative financial value of such training support, when added to the level of discount Wyeth offered, this amounted in total to no more than the level of discounts generally offered by other influenza vaccine suppliers. An example of the terms Wyeth offered was supplied.

At the time when this offer was introduced, Wyeth considered the training support to be a package deal, whereby, as the Authority knew, associated benefits might be provided to purchasers of particular medicines without being in breach of Clause 18.1 of the Code. In Wyeth's view, the transaction as a whole was fair and reasonable, given that the benefits offered were not excessive nor personal in nature, but were relevant to the practice of medicine and directed toward the doctor's practice. Wyeth's understanding of the Authority's interpretation of the supplementary information to Clause 18.1 on package deals was as set out in Case AUTH/170/6/94, where the emphasis was on the reasonableness of the transaction, the distinction being made between business benefits and personal benefits. The Panel's line of thought on this issue was reiterated in Case AUTH/421/4/96.

Wyeth was now aware of Case AUTH/600/8/97, published in the February 1998 edition of the Code of Practice Review, where the Panel gave its interpretation of the meaning of "associated benefit" in that such benefit "had to be relevant to the medicines purchased". Given this recent decision, Wyeth acknowledged that the training support currently offered by it did not now appear to fall within the scope of a "package deal". Accordingly, and subject to the Panel's view on this matter, Wyeth proposed to modify the terms of the training support it offered in future, such that it would be expressly restricted to training relevant to vaccines.

By way of general comment, as would be appreciated, as with a dispensing doctor, the doctor who bought vaccines was both a purchaser and a prescriber. Whilst Wyeth recognised that terms of trade would properly fall for scrutiny within Clause 18 of the Code as to whether they amounted to an inducement, recognition should be given to the difficulties faced by pharmaceutical companies in ensuring that adherence to the Code was on all fours with the competitive terms that were expected of them when dealing with prescribers who were also purchasers of medicines. In this regard, Wyeth awaited the findings of the working party now considering the matter with interest.

In summary, Wyeth acknowledged that, given the recent interpretation of "associated benefit", Wyeth's offer of practice training support did not now appear to fall within the definition of "package deal" in the supplementary information to Clause 18.1 of the Code. Accordingly, subject to the Panel's views on this matter, Wyeth's terms of trade would be modified accordingly.

Wyeth noted that Pasteur Mérieux MSD had also alleged a breach of Clause 2 of the Code in commenting in a less than complimentary fashion about Wyeth's trade practices generally. These comments were, frankly, gratuitous and Wyeth proposed to make no comment other than to say that it did take exception to this blatant attempt to escalate the matter without good cause.

PANEL RULING

The Panel noted that the offer of discounts on the supply of medicines was a well established and recognised practice within the pharmaceutical industry which fell outside the scope of the Code, although the offer of other pecuniary advantages as inducements to prescribe, supply, administer or buy any medicine were prohibited under Clause 18.1. The Panel noted the supplementary information to Clause 18.1 of the Code headed "Package Deals" which stated that package deals might be offered "... whereby the purchaser of particular medicines receives with them other associated benefits, such as apparatus for administration, provided that the transaction as a whole is fair and reasonable." The supplementary information to Clause 18.1 which concerned the provision of medical and educational goods and services could not apply when offers were clearly linked to the promotion of medicines.

The Panel noted that Case AUTH/600/8/97, which had been referred to by both parties, had involved the funding of management training and the level of the funding had been related to agreed levels of usage of the funding company's product. The Panel had considered that it was not a package deal as the associated benefit, the management training programme, was not relevant to the medicine involved. In the Panel's view, the associated benefits, as referred to in the supplementary information to Clause 18.1, had to be relevant to the medicine or medicines purchased. A breach of Clause 18.1 had been ruled.

In the present case the Panel considered that the situation was similar in that the training support was not relevant to influenza vaccine which was the product involved. The benefits were not acceptable under the requirements of Clause 18.1 of the Code and a breach of that clause was ruled.

The Panel accepted that observers might consider the position to be illogical in that the provision of a percentage of sales value in the form of a training grant was unacceptable under the Code whereas the allowance of an extra discount would not have been unacceptable. This was, however, the result of the exemption of discounts from the provisions relating to gifts, a situation which arose from the fact that the Code followed both UK

and European law in this respect.

In relation to the allegation that there had been a breach of Clause 2 of the Code because Wyeth was inducing breach of contract, the Panel did not consider that such conduct in itself was necessarily contrary to the Code. Each case had to be decided on its individual merits. The Panel did not consider that the matter amounted to a breach of Clause 2 and ruled accordingly.

The Panel noted Wyeth's submission that in future it would modify the terms of the training support offered such that it would be restricted to training relevant to vaccines. In the Panel's view to be a genuine package deal within the relevant supplementary information to Clause 18.1, there had to be a logical relationship between the medicine and the training offered. The Panel was not in a position to approve proposed activities.

Complaint received 3 April 1998

Case completed 9 June 1998

CASES AUTH/697/4/98 AND AUTH/698/4/98

GENERAL PRACTITIONER v PARKE DAVIS and PFIZER

Lipitor advertisement

A general practitioner complained about an advertisement for Lipitor issued by Parke Davis and Pfizer which had appeared as an outsert attached to Medical Monitor. The journal had been received in a transparent wrapper and it was alleged that this was an advertisement to the general public, albeit probably not intentional. It was further alleged that the non-proprietary name was not immediately adjacent to the brand name on the first page of the item and nor was the black triangle.

The companies and the publishers of Medical Monitor accepted that the journal had been posted out in an envelope through which the advertisement for Lipitor, which was a prescription only medicine, could be read. Notwithstanding that this was not the fault of Parke Davis and Pfizer, they had to take responsibility for it and the Panel ruled each company in breach. Although the non-proprietary name appeared adjacent to the brand name on pages 2, 3 and 4 of the outsert, it did not appear on page 1, which the Panel considered bore the most prominent display of the brand name, even though it was not the largest. Each company was ruled in breach in that regard. The Panel noted that although the black triangle symbol was referred to in the Code's supplementary information, its inclusion was not actually a requirement of the Code. The Director ruled that there had been no *prima facie* breach of the Code in that regard.

A general practitioner complained about a four page outsert advertisement for Lipitor issued by Parke Davis & Co Limited and Pfizer Limited. The outsert was attached to the spine of Medical Monitor, 15 April 1998, such that it wrapped around both the front and back cover of the journal.

COMPLAINT

The complainant said that he had recently received a copy of the journal Medical Monitor which contained an advertisement for Lipitor. He complained that this advertisement was on clear display to the general public and, in his opinion, breached the Code. He believed that the clauses concerned were:

- Clause 9.7 - the advertisement contained both the name of the product and information as to its usage.
- Clause 4.2 - the non-proprietary name was not immediately adjacent to the brand name (absent from first page).
- Clause 4.2 - the black triangle was not immediately adjacent to the brand name (absent from first page).

As a general practitioner, he took offence at pharmaceutical companies advertising to the general public in this way, albeit probably not intentionally. Patients could come to the surgery demanding a particular brand name medicine simply because they happened to have seen it from such advertisements without the ability to perhaps put the advertisement in its proper context or have the benefit of seeing the prescribing information.

To be fair to the pharmaceutical company, it might be that it was unaware that this journal might not respect the Code but he imagined that the final responsibility rested with the former and not with the latter.

RESPONSE

Parke Davis responded on behalf of itself and Pfizer.

Parke Davis said that it was surprised to learn that Medical Monitor had been sent through the post in a clear wrap. Medical journals to healthcare professionals were sent through the post in opaque envelopes/polywrap which covered any advertising. Parke Davis contacted the publishers of Medical Monitor who were very sorry that an error had occurred on this occasion. They took the Code seriously and were scrupulous in their application of it. They had thoroughly investigated the matter and had identified the error as occurring at the printers. They had assured Parke Davis that they had taken steps to avoid such an occurrence in the future. A letter from the publishers of Medical Monitor and a copy of the letter they had sent to a general practitioner who had written directly to them were supplied.

The complainant had also commented that there was an omission of a black triangle and the product's generic name adjacent to the brand name on the outsert. Parke Davis believed that it had complied with Clause 4.2 of the Code of Practice but was concerned to learn of this criticism. The outsert contained a black triangle and the product's generic name adjacent to the most prominent display of the brand name. In addition, this information appeared on the other side of the outsert. Parke Davis

recognised however, because of the folding of this outsert, that it might have been prudent to include this information with every mention of the brand name. As a result of the concern that had been expressed it would give this particular consideration in future.

PANEL RULING

The Panel noted that the polythene envelope in which Medical Monitor had been posted was transparent on the back. The front of the envelope was divided into four strips; two broad opaque strips which carried postage information and advertised the journal within and two thin transparent strips. The complainant's address label had been stuck to the front of the envelope.

The Panel noted that both Parke Davis and the publishers of Medical Monitor had accepted that the journal had been posted out in an envelope through which the advertisement for Lipitor, a prescription only medicine, could be read. Notwithstanding the fact that the use of a partially transparent envelope was not the fault of Parke Davis and Pfizer, they had to take responsibility under the Code. Each company was ruled in breach of Clause 9.7 of the Code.

In relation to the position of the non-proprietary name, the Panel considered that it was difficult in an item of this type to determine which was the most prominent display of the brand name. In a booklet this would usually be the first appearance, perhaps on the cover, even if the name appeared in larger type elsewhere in the item. In this particular instance, the generic name appeared below the name Lipitor on page 2 of the outsert where the brand name was in the largest type, and again on pages 3 and 4. It did not appear on the first page which lay against the front cover of the journal to which the outsert was attached and which, in the Panel's view, would be the first mention of the product name that readers would see.

Although the Panel had some sympathy with the companies' position in the matter, it considered that the most prominent display of the brand name had to be that on page 1 of the outsert, even though this was not the largest appearance of the name. The Panel noted that Clause 4.1 of the Code stated that the information listed in Clause 4.2 must be provided. Failure to do so would therefore be a breach of Clause 4.1 and not of 4.2. The companies had failed to include the non-proprietary name immediately adjacent to the most prominent display of the brand name as specified in Clause 4.2. The Panel therefore ruled both companies in breach of Clause 4.1 of the Code.

The black triangle symbol was mentioned in the supplementary information to Clause 4.2 of the Code but it was not a requirement of the Code. It had originated as an agreement between the Committee on Safety of Medicines and the ABPI. In consequence the Director determined that there was no *prima facie* case to answer under the Code. Nonetheless, the black triangle symbol should appear once and be located next to the most prominent display of the brand name. The supplementary information gave guidance regarding its size. The Panel noted that the black triangle symbol had not appeared adjacent to the most prominent display of the brand name and asked that the companies be so advised.

Complaint received **20 April 1998**

Case completed **4 June 1998**

CODE OF PRACTICE REVIEW - AUGUST 1998

Cases in which a breach of the Code was ruled are indexed in **bold** type.

674/2/98	General Practitioner v Schwarz Pharma	Promotion of Tylex	No breach	No appeal	Page 88
675/2/98	Nurse v Glaxo Wellcome	Crusaid advertisement	No breach	No appeal	Page 90
676/2/98	**Astra v Wyeth**	**Zoton price comparison**	**Breach 7.2**	**No appeal**	**Page 92**
678/2/98	**Glaxo Wellcome v Merck Sharp & Dohme**	**Launch of Singulair**	**Breach 20.2**	**No appeal**	**Page 94**
679/2/98	Consultant Physician v Merck Sharp & Dohme	Launch of Singulair	No breach	No appeal	Page 97
683/2/98 & 684/2/98	General Practitioner v Bristol-Myers Squibb and Sanofi Winthrop	Aprovel leavepiece	No breach	No appeal	Page 99
686/3/98	**Local Research Ethics Committee v Pharmacia & Upjohn**	**Focus Group meeting**	**Breach 18.1**	**Appeal by respondent**	**Page 101**
689/3/98	**Astra v Wyeth**	**Support for audit**	**Breach 18.1**	**No appeal**	**Page 103**
690/3/98	Hospital Pharmacist v SmithKline Beecham	Kytril mailing	No breach	No appeal	Page 105
691/4/98	**Pasteur Mérieux MSD v Wyeth**	**Inducement to purchase Begrivac**	**Breach 18.1**	**No appeal**	**Page 106**
697/4/98 & 698/4/98	**General Practitioner v Parke Davis and Pfizer**	**Lipitor advertisement**	**Breach 4.1 & 9.7**	**No appeal**	**Page 108**

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, more than fifty 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 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 in connection therewith
- the provision of information to the general public either directly or indirectly
- 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 Philip Cox 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 0171-930 9677 facsimile 0171-930 4554).