PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

CODE OF PRACTICE REVIEW

NUMBER 17 AUGUST 1997

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 1996

The Annual Report of the Prescription Medicines Code of Practice Authority for 1996 has now been published. As previously reported in the Review, there were 102 complaints in 1996 as compared with 104 in 1995, a number in line with the long term average. Over the last few years there have been around 100 complaints each year, although 1994 was exceptional as in that year there was a record number of 145.

A notable feature of the complaints received in 1996 was that for the first time ever the number of complaints from health professionals, at 38, was less than the number received from companies, at 48. There is no apparent reason why this has occurred and it will be interesting to see whether it will prove to be an exception or the beginning of a new trend. Experience in the first six months of 1997 suggests that it may have been exceptional as, by the end of June 1997, a total of 66 complaints had been received and, of these, 33 came from health professionals and only 20 from companies.

Of the 208 rulings made by the Code of Practice Panel in 1996, 165 (79%) were accepted by the complainants and respondents involved, 32 (15%) were unsuccessfully appealed to the Code of Practice Appeal Board and 11 (5%) were successfully appealed. The procedures were changed at the beginning of 1996 to give the complainant who appeals against the rejection of a complaint more information as to the reasons for the decision and the evidence upon which it was based. None of the 9 appeals by complainants in 1995 were entirely successful and only one was partially successful. In 1996, however, of the 10 appeals by complainants, 4 were successful and one partially so. It would appear that the change in procedures has been of assistance to complainants when appealing and it is certainly helpful to them in deciding whether or not they have valid grounds for appeal.

Copies of the Authority's Annual Report for 1996 are available free of charge from the Authority.

Thank you

David Massam, who retired as Director of the Authority at the end of April, would like to thank all his many friends both within and outwith the pharmaceutical industry for the kind letters which he has received wishing him well in his retirement. These were greatly appreciated.

A happy event to come

Emer Flynn (née O'Reilly), who joined the ABPI in 1990 and has been with the Authority since its inception in 1993, started her maternity leave in July. The Authority wishes her and her family well.

During her absence, Vicky Meyrick, who joined the Authority in 1995, takes over Emer's responsibilities, including the organisation of seminars on the Code of Practice.

Voluntary admissions

Pharmaceutical companies occasionally advise the Authority that they have erroneously used material in breach of the Code. Such an admission usually relates to a technical matter, such as the omission of the price in prescribing information and action has usually already been taken to correct the breach. In such circumstances, the Authority has advised the company that if a complaint were to be received it would have to be considered in the usual way but otherwise no further action has been taken.

Recently, however, a company advised the Authority of a breach which could potentially be very serious. The Authority advised the company that if a complaint were made it would be considered in the usual way and various steps were suggested for the company to take in order to prevent a recurrence. The Authority did not take any further formal action but sought guidance from the Code of Practice Appeal Board as to how to handle such matters in the future.

The Appeal Board thought that the voluntary admission of a potentially serious breach would be a rare event. It agreed with the Authority's current position on matters such as the omission of the price in prescribing information. The Appeal Board's advice to the Authority was that companies should be cautioned that, if they were going to admit to a serious breach of the Code, then this information might be used as the basis for a formal complaint against them. Companies should be asked to provide details of the action taken to correct the admitted breach and the Director of the Authority should then decide whether or not to initiate a formal complaint about the matter.

The Appeal Board considered that it would be helpful to draw this to the attention of companies.

Pharmacists and the acceptance of gifts

The Law and Ethics Bulletin is an occasional feature prepared by the Royal Pharmaceutical Society of Great Britain's Law Department to highlight problems and enquiries currently being handled. The Bulletin published in The Pharmaceutical Journal on 21 June, 1997, dealt with the acceptance of gifts and inducements by pharmacists.

The Society stated that pharmacists accepting items such as gift vouchers, bonus points, discount holidays and sports equipment from pharmaceutical companies and distributors would contravene Principle 3 of the Society's Code of Ethics. Pharmacists were therefore advised not to participate in such offers.

Protocol of agreement

When the Authority was established by the ABPI in 1993, the principal purpose was to separate the administration of the Code of Practice and, in particular, the system for adjudicating upon complaints made under the Code, from the operation of the ABPI itself. Nonetheless, the Authority remains part of the ABPI and critics often query whether the Authority can really operate in an impartial manner.

With a view to establishing more clearly the relationship between the Authority and the ABPI, the Authority and the Board of Management of the ABPI have now agreed a protocol which sets out that relationship in detail.

The Authority does not suffer from any interference on the part of the ABPI and it is confident that the protocol will help to ensure that this will continue.

Copies of the protocol of agreement are available upon request.

New Code for 1998?

It is anticipated that there will be a revised version of the Code of Practice for the Pharmaceutical Industry operative as from the beginning of 1998.

Proposals for the changes to be made will be sent out for consultation to pharmaceutical companies and also to the British Medical Association, the Medicines Control Agency, the Office of Fair Trading and the Royal Pharmaceutical Society of Great Britain.

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.

Forthcoming Code of Practice seminar dates are:

Tuesday, 21 October 1997
Friday, 21 November 1997
Friday, 12 December 1997

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 Vicky 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 Vicky Meyrick (0171-930 9677 extn 1443).

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

Heather Simmonds 0171-747 1438

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.

CASE AUTH/448/7/96

LOREX SYNTHÉLABO v YAMANOUCHI

Promotion of Flomax

Lorex Synthélabo complained about the promotion of Flomax by Yamanouchi.

A claim "Superselectivity and the treatment of BPH" was ruled to be a claim for a special merit for Flomax which had not been adequately substantiated in breach of the Code. The Panel's ruling was upheld by the Appeal Board.

A claim that Flomax was 61 more times selective than other alpha$_1$ blockers was ruled to be misleading as the clinical benefit from using a selective agent was in part, theoretical. The Panel's ruling was upheld by the Appeal Board.

A claim regarding a reduction in the likelihood of postural hypotension and syncope was ruled to be misleading as the claim as worded went beyond the available data. The Panel's ruling was upheld by the Appeal Board.

The Panel ruled that a claim "improved flow from day 1" had not been substantiated by the limited data provided. The Appeal Board overturned the Panel's ruling and ruled no breach of the Code as further details had been supplied for the appeal.

A letter to wholesalers was ruled in breach by the Panel as prescribing information had not been printed on the letter itself. No breach of the Code was ruled regarding an allegation that the claims were not supportable. No breach was ruled regarding an alleged failure to give references. The letter did not refer to published studies and references were not required.

Lorex Synthélabo Limited submitted a complaint about the promotion of Flomax by Yamanouchi Pharma Ltd. The material at issue was a detail aid (YAM 56947) which was the subject of four allegations and a letter which was the subject of an allegation.

1 Claim "Superselectivity and the treatment of BPH"

COMPLAINT

Lorex Synthélabo alleged that the claim suggested that Flomax (tamsulosin) had some special merit, quality or property which was not justified by currently available information. The company knew of no evidence that α_{1A} blockade led to additional clinical benefit over other alpha blockers. Breaches of Clauses 7.3 and 7.8 were alleged.

RESPONSE

Yamanouchi said that many subtypes of α_1 adrenoceptors had been identified. Over recent years it had been shown that the α_{1A} adrenoceptor subtype predominated both numerically and functionally in the prostate and was responsible for contraction of prostatic smooth muscle.

The company submitted that the statement "superselectivity and the treatment of BPH" was not therefore a claim but merely described the fact that tamsulosin was more selective for the α_{1A} adrenoceptor subtype than any other alpha adrenoceptor antagonist used in the management of benign prostatic hyperplasia (BPH). The summary of product characteristics (SPC) stated that "Tamsulosin binds selectively and competitively to the post synaptic alpha$_1$ receptors, in particular to the subtype alpha$_{1A}$". The company submitted that the degree of selectivity was well proven. The Lepor (1995) review (referred to by the complainant in relation to point 2 below) included the statement "Tamsulosin is the only long-acting α_1 - blocker under clinical investigation that exhibits selectivity for the α_{1C} - AR". Yamanouchi explained that the α_{1C} adrenoceptor (α_{1C} - AR) had subsequently been renamed the α_{1A} - AR.

PANEL RULING

The Panel considered that the statement was a claim and noted that it appeared on the front page of the detail aid and that similar claims appeared inside. It considered that the claim was a strong one. The claim was too sweeping given the limited clinical data and the fact that any clinically significant benefit from the use of a selective agent was still in part theoretical. In this regard the Panel noted that the Lepor (1995) review stated that "There are insufficient data to determine whether the α_{1C} - selective properties of tamsulosin will have clinical benefits. The clinical benefits of tamsulosin and other α_{1C} selective compounds will depend upon the α_1 - AR that mediates efficacy, vascular effects and adverse events".

The Panel considered that the claim implied a special merit for Flomax which had not been adequately substantiated. A breach of Clause 7.8 of the Code was ruled.

APPEAL BY YAMANOUCHI

Yamanouchi submitted that the use of the term "superselectivity" was intended to describe the greater selectivity of tamsulosin for the α_{1A} receptor compared to the α_{1B} receptor. The term was used to convey the message that tamsulosin was the most selective alpha antagonist currently available. The term was coined in deference to the notion that α_1 adrenoceptor antagonists were described as selective in relation to their action on α_2 receptors. It thus followed that an agent which demonstrated selectivity for a subtype of the α_1 receptor should be described as superselective. It was well accepted that in a similar vein the term cardioselectivity was used in the past to indicate that medicines were more selective for the β_1 receptors than the β_2 receptors. It was not strictly true to use the term "prostate selective" in relation to tamsulosin as α_{1A} receptors existed in other organs, for example, the liver. The term "prostate selective" had been widely used by clinicians in publications. Obviously α_{1A} adrenoceptor antagonists would also affect these α_{1A} receptors as would non subtype selective α_1 adrenoceptor antagonists. Hence the focus was on describing the selectivity of tamsulosin for the different alpha subtypes. The statement

"Superselectivity in the treatment of BPH" did not make a claim for tamsulosin. It referred factually to how an improved subtype specific selectivity might relate to the treatment of BPH. Doctors were left to decide if the greater selectivity was likely to offer them any specific advantage in clinical practice.

Yamanouchi submitted that the concept of superselectivity was drawn from published literature and provided a copy of a paper by Professor Chapple, a consultant urological surgeon, which used the term superselectivity in connection with tamsulosin specificity for the α_{1A} receptor. Another article by Rabasseba supported the concept of increased selectivity of tamsulosin for prostate α_1 receptors. The company also provided personal communications from three consultant urologists to support the use of the term superselective.

The company said that the use of the term "superselectivity" had been created by Yamanouchi to describe the pharmacological effect. It was a marketing term and it was for the medical profession to decide whether or not to use the term. It was merely a way of describing a subgroup.

APPEAL BOARD RULING

The Appeal Board noted that the front of the detail aid had the statement "Superselectivity and the treatment of BPH". Each double page was headed "Once daily Flomax" with the subheading "the first α_{1A} blocker: superselectivity in the treatment of BPH". This also appeared on the final page of the detail aid.

The Appeal Board considered that the term "superselectivity" was a marketing term rather than a generally accepted description of a pharmacological effect. The Appeal Board noted that the term was not widely used in the literature - it could only find one mention of it in the published papers supplied by Yamanouchi. The letter from one of the consultant urologists stated "The choice of terminology obviously should be by consensus within the profession, but meanwhile the term superselectivity has been advanced". The Appeal Board did not object to the term per se but did object to the way it had been used in the detail aid. The use of the term had not been limited to describing the pharmacological properties of tamsulosin but had been used to imply that the product was "super" or very good. The Appeal Board agreed with the Panel that the term had been used to imply a special merit which had not been substantiated. The Appeal Board therefore upheld the Panel's ruling of a breach of Clause 7.8 of the Code.

The appeal on this point therefore failed.

2 Claim "Flomax MR is up to 61 times more selective than other alpha1 blockers . . ."

COMPLAINT

Lorex Synthélabo said that the claim was based on a ratio of α_{1A} to α_{1B} selectivity. The data quoted in the detail aid were not based on all the available data but selective to one reference (Foglar 1995). Specific selectivity for the α_{1A} receptor alone might not indeed be beneficial. It was currently unknown which alpha subtype receptor(s) might mediate side effects associated with alpha blockade and therefore the clinical benefits of receptor subtype selective medicines was theoretical. Lorex Synthélabo referred to the Lepor (1995) review.

RESPONSE

Yamanouchi explained that the claim in question came from a published paper by Foglar in which the Ki (dissociation constant) of tamsulosin for the α_{1C} (now α_{1A}) adrenoceptor was quoted as 0.035nM and the Ki of tamsulosin for the α_{1b} (now α_{1B}) adrenoceptor was quoted as 0.7 nM. Hence tamsulosin was 20 times more selective for the α_{1A} than for the α_{1B} (20 x 0.035 = 0.7). The corresponding data for alfuzosin were 4.2nM and 1.4nM. Hence alfuzosin was 0.33 times as selective for α_{1A} than α_{1B}, or 3 times more selective for α_{1B} than α_{1A}. Therefore the relative selectivity of tamsulosin: alfuzosin was 20: 0.33, tamsulosin being 60.6 times (60.6 x 0.33 = 20) more selective for α_{1A} than alfuzosin. Lorex Synthélabo had quoted a paper by Graham (1996) in its correspondence with Yamanouchi which confirmed the very much higher selectivity of tamsulosin for the α_{1A} subtype than α_{1B}, in contrast to alfuzosin.

Yamanouchi said that there were references that stated that α_{1A} adrenoceptor was the receptor in the prostate and was responsible for contraction of prostate smooth muscle (Abrahams *et al*, 1995). The paper went on to present data on a pan European, placebo controlled trial and concluded that tamsulosin was effective with a favourable cardiovascular safety profile. The paper attributed the findings to the selectivity, ending with "Tamsulosin appears to have a favourable cardiovascular safety profile compared with placebo, with no apparent effects on blood pressure and pulse rate, and does not require titration, probably because it is selective for the α_{1C} adrenoceptor [now designated the α_{1A} adrenoceptor] subtype predominantly present and functional in the human prostate".

Yamanouchi noted that no specific breaches of the Code had been alleged but it believed the data was consistent in showing that tamsulosin had superior selectivity for the α_{1A} adrenoceptor and that there had been no breach of the Code.

PANEL RULING

The Panel examined the Foglar study to which the claim was referenced. It noted that the dissociation constants, Ki, had been calculated using cells expressing the rat α_{1A}, the hamster α_{1B} and the human α_{1C} adrenoceptors. It appeared to the Panel that the selectivity calculations were based on the hamster α_{1B} dissociation constant and the human α_{1C} dissociation constant. The Panel was unsure of the relevance of hamster α_{1B} adrenoceptors to the human situation. It appeared that the calculations were a mixture of human and hamster *in vitro* data. This had not been made clear in the detail aid.

The Panel noted that Lorex Synthélabo had alleged that the claim was not based on all the available data. The complainant had not provided any data to support the complaint. Data had been referred to when the companies were discussing this allegation prior to complaining to the Authority. The Graham paper referred to by Yamanouchi

said that most of the α_1 adrenoceptor antagonists used in the treatment of BPH, including afluzosin, did not show *in vitro* selectivity towards any one of the α_1 adrenoceptors cloned to date. It went on to say that in contrast a certain degree of selectivity was exhibited by tamsulosin ... for the α_{1A} subtype and "In this context, it is possible that drugs which might interact with a functional prostatic α_1 subtype different from that in the vasculature could offer α_1 adrenoceptor subtype selective antagonists for the treatment of BPH with improved therapeutic profiles".

The Panel considered that its views about the clinical relevance of selectivity made in point 1 above applied similarly to this allegation. It considered that the claim was misleading given that the clinical benefit from using a selective agent was still in part theoretical.

A breach of Clause 7.2 of the Code was ruled.

APPEAL BY YAMANOUCHI

Yamanouchi said that the claim at issue was a simple statement of fact which was supported by the graph which appeared below it in the detail aid. The company said that in the prostate 70% of the a_1 receptors were α_{1A}. The remaining 30% of α_1 receptors were a possible mixture of α_{1B}, and other, possibly as yet unidentified a receptors. Tamsulosin was more selective for the α_{1A} receptors as stated in the summary of product characteristics (SPC). Yamanouchi was simply stating that based on dissociation constants, tamsulosin bound more selectively to the α_{1A} receptor than the α_{1B} receptor.

The company referred to three studies from which the relative selectivities of tamsulosin and alfuzosin had been calculated. The figures were 60.6 in the Foglar paper, 144.1 in the Graham papers (which had been provided to Yamanouchi by Lorex Synthélabo) and 115.2 in the Michel paper.

For work evaluating the relative receptor dissociation constants upon which the calculations were based, it was normal to use animal tissue as a source of receptor. While it was possible and relatively easy to obtain human prostate tissue to provide the α_{1A} receptors it was not as easy to obtain samples of human internal iliac arteries for the a_{1B} receptors. The work done in determining cardioselectivity of betablocking agents widely used receptors derived from animal tissue.

The company said that a tenfold difference meant that there was likely to be a clinical benefit. The company agreed that this likely benefit had not been proven.

APPEAL BOARD RULING

The Appeal Board accepted that the claim was factually correct and that it was not an unfair reflection of the data given the studies referred to by Yamanouchi.

The Appeal Board noted that when ruling on specific claims in a detail aid, the overall context and what it would mean to the audience were important considerations.

The Appeal Board considered that the claim together with the graph implied that the difference between the selectivity for α_{1A} receptors of tamsulosin and the other products mentioned in the graph alfuzosin, doxazosin, indoramin, prazosin and terazosin implied that tamsulosin was an improvement compared to the other products. This was misleading given that the benefits of using a selective agent were in part theoretical. The Appeal Board therefore upheld the Panel's ruling of a breach of Clause 7.2 of the Code.

The appeal on this point therefore failed.

3 Claim "The alpha$_{1A}$ selectivity of Flomax MR reduces the likelihood of postural hypotension and syncope"

COMPLAINT

Lorex Synthélabo alleged that the claim was unsupportable. Data on file supplied by Yamanouchi on its three month comparative study, tamsulosin once daily versus alfuzosin 2.5 mg twice daily or three times daily, showed a greater number of patients (4 (3%)) with postural hypotension on tamsulosin than on alfuzosin (2 1%)). The claim therefore breached Clauses 7.2 and 7.3 of the Code.

RESPONSE

Yamanouchi said that many authors stated that α_{1A} selective adrenoceptor antagonists were theoretically an advantage. There were also many papers stating that an α_{1A} selective adrenoceptor antagonist might be useful in the management of BPH as it should be effective with reduced risk of cardiovascular side effects. There were also data to show that the α_{1B} adrenoceptor could be found in the internal iliac arteries, indicating that these receptors might mediate the cardiovascular response to alpha antagonism.

In all Yamanouchi's studies, the number of patients experiencing cardiovascular side effects on tamsulosin was equivalent to placebo. The Abrams paper presented the data on a pan European placebo controlled trial that concluded that tamsulosin was effective with a favourable cardiovascular safety profile. It attributed the finding to the selectivity ending with the words "Tamsulosin appears to have a favourable cardiovascular safety profile comparable with placebo, with no apparent effects on blood pressure and pulse rate, and does not require dose titration, probably because it is selective for the α_{1c} adrenoceptor [now designated the α_{1A} adrenoceptor] subtype predominantly present and functional in the human prostate".

PANEL RULING

The Panel noted that Yamanouchi had not addressed the complainant's point regarding the greater number of patients with postural hypotension on tamsulosin than on alfuzosin. The Panel noted that the data given by the complainant were odd, given that the letter of complaint said that "the greater number of patients (4 (3%)) with postural hypotension on tamsulosin than on alfuzosin (2 1%))". The Panel noted that the alfuzosin figures should perhaps have been (2 (1%)). In the Panel's view, given the apparent number of patients, the difference was unlikely to be a significant difference. The Panel noted that Yamanouchi itself had referred to the fact that the α_{1A}

selective adrenoceptor antagonist was theoretically an advantage and the product should be effective with reduced risk of cardiovascular side effects. The Panel did not accept that there was sufficient data to support the claim as worded which went further than the available data. The Panel considered that the claim was misleading and ruled a breach of Clause 7.2 of the Code.

APPEAL BY YAMANOUCHI

Yamanouchi said that there appeared to have been some confusion in relation to this allegation. The Yamanouchi study comparing alfuzosin and tamsulosin showed that four patients in the tamsulosin group and one patient in the alfuzosin group experienced postural hypotension. None of the statistical tests implied that there were any statistical differences between alfuzosin and tamsulosin with respect to this side effect.

The claim was used as a possible explanation of why the incidence of hypotension and other related cardiovascular effects related to tamsulosin were low. As shown in the clinical papers, the incidence of cardiovascular side effects occurring in the tamsulosin group was comparable to placebo. Hence the claim that tamsulosin had a low incidence of cardiovascular side effects was well substantiated from the published literature and might be attributed to its greater degree of subtype selectivity.

In the study queried by Lorex Synthélabo, Yamanouchi also compared the blood pressure effects of tamsulosin and alfuzosin. It was clearly demonstrated that alfuzosin had a statistically significantly greater effect on blood pressure than tamsulosin. Based on this evidence, the likelihood of postural hypotension and syncope occurring in patients receiving tamsulosin must be less than on other alpha antagonists, even alfuzosin.

A more recently published paper (Haraba *et al*) investigated the effects of tamsulosin 0.2mg, doxazosin 1mg and placebo on the α_1 adrenoceptor blockade on fingertip and dorsal hand venous adrenoceptors stimulated by cold water. The reduction in fingertip blood flow after cold stimulation was significantly smaller after treatment with doxazosin ($p < 0.01$) than after tamsulosin or placebo. Hence that doxazosin obtunded the vasoconstriction induced by cold, whereas tamsulosin and placebo did not. The data suggested that the alpha blocking effect on fingertips vasculature was lower for tamsulosin than doxazosin. If this was true in other parts of the body vasculature the potential for tamsulosin to cause vasodilation and hypotension was reduced. This would appear to be an effect of the α_1 selectivity of tamsulosin.

Yamanouchi submitted that from the data the selectivity of tamsulosin and the α_{1A} adrenoceptor would appear to reduce the effect of the alpha blockade in the vascular tree and hence reduce the likelihood of vasodilation, postural hypotension and syncope occurring.

APPEAL BOARD RULING

The Appeal Board noted that the SPC listed postural hypotension as an undesirable effect. The claim in question appeared beneath the graph referred to in point 2 above. The context implied that the products mentioned in the graph had a problem with postural hypotension and syncope whereas Flomax did not. The Appeal Board accepted that it was likely that the α_{1A} selectivity of Flomax would probably reduce the likelihood of postural hypotension and syncope but that was not what the claim said. The Appeal Board agreed with the Panel that there was not sufficient data to support the claim as worded which went further than the available data. The Appeal Board upheld the Panel's ruling that the claim was misleading in breach of Clause 7.2 of the Code.

The appeal on this point therefore failed.

4 Claim "Improved flow from day 1"

COMPLAINT

Lorex Synthélabo said that this claim was referenced to data on file OM96014. However the data when requested made no mention of improved flow from day 1. The study examined visits several weeks apart with no data apparently collected after one day of treatment. A breach of Clause 7.3 of the Code was alleged.

RESPONSE

Yamanouchi said that improved flow from day 1 was supported by an abstract by Lepor (1995). In this study the effects of the first dose were studied and a statistically significant effect on flow rates was detected. The study stated "The 0.4 mg dose was shown to be statistically and clinically effective with a rapid onset of action based upon the Qmax after the first dose".

PANEL RULING

The Panel queried whether there had been an error in referencing the claim at issue (which appeared on the back page) to data on file. Perhaps it should have been referenced to the Lepor abstract. The Panel noted that the data on file had not been provided. Another claim which appeared inside the detail aid "Improvement in flow on the first day of treatment" followed by the claim "Maximum urinary flow rate (Qmax) increased after the first dose" was referenced to the abstract by Lepor (1995).

The Panel examined the abstract and noted that it only provided limited data. No detailed results or statistics were provided. The Panel considered that the abstract was inadequate to substantiate the claim at issue. The Panel therefore ruled a breach of Clause 7.3 of the Code.

APPEAL BY YAMANOUCHI

Yamanouchi said that the reference used in the detail aid was for an abstract as the whole study report and statistical tables were very unwieldy. The data came from study YM617 US92-03A. The study was a randomised double blind multicentre parallel group design comparing placebo to 0.4 and 0.8mg of tamsulosin. Patients were initially entered into a 4 week single blind placebo run in phase. During this 4 week period visits 1 to 3 occurred. At visit 4 (week 5) the first dose of trial medication was administered. All patients received 0.4mg for the first week. Following the first dose patients were observed for 8 hours. Data collected on routine vital signs, orthostatic tests and uroflowmetry which was conducted 4-8 hours

after the first dose.

The data collected from the uroflowmetry demonstrated that the average maximum flow rate significantly increased compared to baseline at this first assessment. The p value comparing tamsulosin to placebo was $p < 0.001$. The mean change in flow rate was 1.78ml/sec. The placebo group had a mean increase in maxflow rate of 0.71ml/sec.

The company referred to a paper by Schulman which was a review of the effect of the first dose of tamsulosin. This data further supported the claim.

APPEAL BOARD RULING

The Appeal Board noted that the only data provided to the Panel was the Lepor abstract which gave brief details of two Phase III clinical studies (US92-03A and US93-01). Further details had been provided in the papers for the appeal. The Appeal Board accepted that the company had data to substantiate the claim at issue and therefore ruled no breach of the Code.

The appeal on this point was therefore successful.

5 Letter headed "Flomax MR: New product information"

COMPLAINT

Lorex Synthélabo said that the letter from the product manager made a number of claims completely unsupported by references. A breach of Clause 7.5 of the Code was alleged. The claims were also not supportable; for example, antihypertensive agents were not contraindicated with alfuzosin. A breach of Clause 7.3 of the Code was alleged. In addition despite a statement that the SPC was enclosed no prescribing information was included. A breach of Clause 4.1 of the Code was alleged.

RESPONSE

Yamanouchi explained that the letter was sent to wholesalers and not to members of the medical and pharmacy professions for information on the product. All of the information in the letter was supportable and available on request. At no point in the letter did it state that alfuzosin was contraindicated in patients receiving other antihypertensive treatment. As an SPC was enclosed with the letter there was no breach of Clause 4.1.

PANEL RULING

The Panel noted that factual, accurate, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings, trade catalogues and price lists, were exempt from the Code providing they included no product claims (Clause 1.2). In the Panel's view, because the letter included product claims it was not exempt from the requirements of the Code. The Panel noted that the audience was wholesalers but the purpose of the letter was to promote the supply or sale of Flomax. It therefore came within the scope of the Code.

With regard to the requirement for prescribing information, the Panel noted the supplementary information to Clause 4.1 of the Code which stated that the inclusion of an SPC or data sheet did not suffice to conform with the provisions of Clause 4.1. Each item had to be able to stand alone. The prescribing information needed to be printed on the letter itself. The Panel ruled a breach of Clause 4.1 of the Code.

The Panel noted that the Xatral (alfuzosin) data sheet listed under the heading contraindications, "patients taking other alpha-blockers" and under the heading interactions that "Concomitant use with other α- 1 - receptor blockers should be avoided and antihypertensive agents should be used with caution because of the risk of a hypotensive effect".

The Panel noted that the letter said "The majority of the other products used for treatment in BPH were originally developed as antihypertensive agents. Consequently, their concommitant use with other antihypertensive agents is contra-indicated". The letter did not state that alfuzosin was contraindicated for patients receiving other antihypertensive treatment. The Panel therefore ruled no breach of Clause 7.3 of the Code.

The Panel noted that references were only required by Clause 7.5 of the Code when material referred to published studies. All material had to be capable of substantiation which must be provided upon request but there was no need to reference material routinely unless it mentioned a published study. The Panel noted that the letter did not refer to any published studies and therefore no breach of Clause 7.5 was ruled.

The appeal was held in December 1996. The material ruled in breach was withdrawn from use on 10 January 1997. The delays in completing the case related to problems with the terms of the requisite form of undertaking and assurance which was prolonged by the cancellation of a meeting of the Appeal Board.

Complaint received **31 July 1996**

Case completed **4 June 1997**

CASE AUTH/481/12/96

NO BREACH OF THE CODE

CCLpk v LEO

Use of treatment protocol

CCLpk complained about Leo's use of a patient treatment protocol which it had developed for one particular hospital and which Leo had financed. It was alleged that without reference to CCLpk, and without permission, Leo had made copies of the prerelease version and its sales representatives had used them in hospital pharmacies and other departments across the country.

The Panel did not consider that it had been able to get a clear picture of the disagreement between the parties despite months of trying. It seemed to be basically a contractual dispute rather than a substantive Code matter. The Panel did not consider that the Code had been breached.

COMPLAINT

CCLpk Limited, health care economists, said that it carried out work on behalf of an NHS Trust which involved the production of a Business Case which resulted in an improvement and change in a patient treatment protocol. The study was financed by an interested party, Leo Pharmaceuticals, which was keen to learn from the new approach as it was a significant change from the very traditional prescription approach. The terms and conditions of the contract were clearly stated and agreed from the outset. A copy was supplied to the Authority.

Before the final "release version" of the Business Case was issued, a version of the Business Case at that time was prepared and issued for Leo's prearranged study day for its senior marketing and sales force and was stated to be for "internal use only".

Some time later, without reference to CCL and in disregard of the Code of Practice and, incidentally, the contract and copyright, Leo made further copies of the prerelease version and sales representatives used them and referred to them in hospital pharmacies and other departments across the country. The hospital where the work was carried out actually complained to its chief executive officer. After several requests to withdraw the work from circulation, Leo had continued to refuse to convince CCL or the hospital that no other copies were in circulation. There was extremely serious concern about this misuse of data. No permission was ever given by CCL to copy the work.

CCL alleged that there had been breaches of Clause 2 of the Code as discredit to and reduction in confidence in the industry had been voiced to both hospital staff and CCL, of Clause 9.5 which stated that reproductions of official documents must not be used for promotional purposes unless permission had been given in writing by the appropriate body, of Clause 11 because there was clear evidence that there had been the provision of unsolicited reprints, of Clause 12 because no permission had been given for the distribution of the prerelease version, of Clause 14 because that stated that promotional material must not be issued unless it was in final form to which no subsequent amendments could be made, of Clause 15 relating to representatives and of Clause 16 because CCL did not believe that Leo's staff were fully conversant with the requirements of the Code.

CCL also made reference to the guidelines on company procedures relating to the Code of Practice which were set out in the Code of Practice booklet.

After some delay, CCL responded to the Authority's request to see a copy of the Business Case, permission having been sought by CCL from the Trust.

In answer to a number of questions subsequently raised by the Authority, CCL advised that the price quoted in the protocol for low molecular weight heparin was taken to be representative of prices in the market place and in this instance the price was supplied by Leo. The copy of the protocol which had been supplied by CCL to the Authority was the prerelease version as consistent with CCL's terms and conditions and project management documentation. CCL would always give clear guidance as to how the final release protocol should be presented to third parties. Preparatory measures were initiated with Leo to ensure that correct usage of the protocol would take place once the final release version was authorised. CCL did not, and could not, authorise the release version until written agreement with the hospital and the company had been reached. No tripartite agreement had yet been reached and signed off in accordance with CCL's internal quality control.

RESPONSE

The initial response from Leo Pharmaceuticals stated that the continuing debate between CCL and Leo did not fall within the scope of the Code in that it did not concern the promotion of a medicine to members of the UK health professions. The protocol referred to concerned the development of general guidelines for the treatment of deep vein thrombosis within a particular hospital. No specific product was mentioned by name. Subject to the approval of the hospital management the guidelines might have been made available to other hospitals for their consideration. The protocol had not been approved.

Following an approach by the Authority for further information, Leo said that it was involved because it was approached by CCL to fund a study examining the financial implications of changing from an in patient treatment protocol for deep vein thrombosis (DVT) to an ambulatory service. This was an area in which Leo (along with many other companies) had a product interest. No use was being made of the document by Leo. Despite express assurance by CCL that the Trust had approved its use by Leo, it subsequently discovered that no such approval had been given. At the request of the Trust, it immediately stopped using the document. It was important to emphasise that there was no dispute between Leo and the Trust.

In answer to the question as to what was the purpose of

Leo's activity, the company said that the document was a financial analysis of various treatment protocols for DVT. It was important to understand that, if the protocol were to describe financial benefits accrued to the NHS, it would involve a way in which patients were managed. This would be to the benefit of the patients, the Trust, and those companies supplying products in the class concerned, including heparins.

There was no prerelease version. The protocol was presented to Leo by CCL as being authorised for release. Indeed, CCL came to Leo's offices to give clear guidance as to how the protocol should be presented to third parties. Leo assured the Authority that no product was mentioned by name. The document was being used by representatives to help explain the financial implications of a range of treatment regimes.

The draft contract which had been sent to the Authority by CCL was never agreed by Leo and never signed.

In response to a further letter from the Authority which referred to the individual allegations made by CCL, Leo said in relation to the allegation concerning Clause 2 that the document was all about exploring the financial implications of a range of treatment options within the management of patients with DVT.

In relation to Clause 9.5 and the question of whether the protocol was an "official document", Leo said that the document was produced by CCL with the cooperation of the Trust and was not therefore an official document as meant by Clause 9.5.

The document was never used for promotional purposes. It was used as part of a discussion between certain Leo representatives and interested third parties, usually pharmacists who had expressed interest in the implications of the protocol and the management of DVT in their hospitals or health authorities.

In answer to the question as to whether written permission had been given for Leo's use of the document, Leo said that permission for use of the document by Leo was given by CCL. Leo was misled by CCL into believing that the Trust had agreed to the use of the document by Leo. This was discovered not to be the case whereupon Leo ceased to use the document and gave an undertaking to the Trust not to distribute further copies. There was no dispute between Leo and the Trust, with which it had a cordial relationship.

In relation to Clause 14, the protocol was not used as promotional material, was not promotional material and was not therefore certified. In relation to Clause 15, instruction in the use of the protocol was given orally by CCL to certain of Leo's representatives. There was no briefing material.

Leo emphasised that the protocol was not promotional and was not intended to be promotional. Its intentions in developing and using it were to involve itself with its customers in the NHS in an attempt to improve patient care and improve the cost effectiveness of this care. Drug usage or drug cost was an insignificant part of the process of change which might accrue from the adoption of one or other of the treatment regimes.

PANEL RULING

The Panel noted that the guidelines on company procedures relating to the Code of Practice which were set out in the Code of Practice booklet, and to which CCL had referred, were not part of the Code of Practice and could not be breached. They merely formed guidance as to the administrative means by which companies might seek to avoid breaching the Code.

Three months had been expended in trying to get a clear picture of the dispute between the two companies but the Panel considered that the factual position was still far from clear as the information provided by CCL and by Leo was inconsistent in many respects. It seemed to the Panel that the matter was basically a contractual disagreement between CCL and Leo rather than being substantively a Code of Practice matter. The Panel examined the allegations in turn.

Alleged breach of Clause 2. The Panel did not consider that the facts at its disposal in any way indicated that there had been a breach of Clause 2 and ruled accordingly. .

Clause 9 - Clause 9.5 stated that reproductions of official documents must not be used for promotional purposes unless permission had been given in writing by the appropriate body. The Panel did not consider that the prerelease version of the document was an "official document" as meant by the Code. No breach was ruled.

Clause 11 - Provision of Reprints. This clause referred to reprints of articles in journals and was not considered relevant by the Panel. No breach was ruled.

Clause 12 - Distribution of Promotional Material. There was no reason to suppose that any material was provided to persons whose interest in the material could not be reasonably assumed. No breach was ruled.

Clause 14 - Certification of Promotional Materials. The Panel did not consider that the protocol was promotional material. No breach was ruled.

Clause 15 - Representatives. There was no evidence to show that Leo's representatives had breached the Code and it was ruled that there had been no breach of Clause 15.

Clause 16 - Training. The Panel could see no reason to suppose that Leo's staff were inadequately trained in relation to the Code and ruled that Clause 16 had not been breached.

The Panel considered that the only potential breach of the Code demonstrated in the complaint was that Leo representatives might have used the non-promotional protocol for a promotional purpose in such a manner as to breach the Code. The protocol did refer in a number of places to low molecular weight heparin and its cost. There was, however, no evidence that there had been improper use of the protocol by Leo representatives and the Panel ruled that there had been no breach.

Complaint received **12 December 1996**

Case completed **24 April 1997**

CASE AUTH/486/1/97

CONSULTANT DERMATOLOGIST v WYETH

Letter on Minocin

A consultant dermatologist complained about a letter referring to Wyeth's product Minocin (minocycline) which had been circulated to doctors by Wyeth.

The complainant had been asked by Wyeth to write to local doctors because many patients who were well established on minocycline for their acne had been taken off it because of worry about lupus erythematosus like symptoms. The letter had, however, been circulated more widely than the consultant's immediate catchment area and had been retyped with a different date and title. The title had changed from "Should minocycline ever be prescribed for the treatment of acne" to "Minocycline for the treatment of acne". The Trust logo of the hospital at which the consultant was based had been reproduced on the letter and the envelope.

The Panel considered the change in the title to be a serious matter as it completely changed its meaning. It was up to anyone reproducing a letter in this way to have a high standard of checking. The copying of the Trust logo was also a serious matter, particularly on the envelope as this was a tactic likely to ensure prompt attention by recipients. The Panel considered that high standards had not been maintained and that the use of the logo on the envelope and the failure to reveal Wyeth's role amounted to disguised promotion. These rulings were accepted by Wyeth.

The Panel also considered that the circumstances had brought discredit upon the industry and so ruled. This ruling was appealed by Wyeth but confirmed on appeal by the Code of Practice Appeal Board.

This complaint concerned a letter which had been circulated by Wyeth to doctors in a certain area of Birmingham. The letter referred to the Wyeth product Minocin (minocycline). It appeared to be on the notepaper of an NHS Trust and was headed "Minocycline for the treatment of acne". The letter referred to adverse publicity about the side effects of minocycline which had appeared in the press and which had brought to a head the question of whether minocycline should be prescribed for the treatment of acne. The final sentence of the letter stated "I personally would have no hesitation in prescribing Minocin if I felt that it was clinically indicated and my views on this have not changed since the publication of the clinical paper by Professor Emery et al". The letter was signed by the complainant, a consultant dermatologist.

COMPLAINT

The complainant said that he had been asked by the company's local representative to jot down some comments about the safety of minocycline. The reason he had been asked to do this was because many patients who were well established on minocycline for their acne were being taken off it because of the worry about lupus erythematosus like syndromes.

The complainant then discovered that the letter had been circulated more widely than the immediate catchment population and had been retyped with a different date applied and a different title. The original letter was headed "Should minocycline ever be prescribed for the treatment of acne" whereas the letter sent out by Wyeth was headed "Minocycline for the treatment of acne". This had been done without any discussion and, when the complainant approached Wyeth, the company suggested that it was merely a typographical error.

The complainant pointed out that the letter had been reproduced in minute detail and that the Trust logo was copied on to plain white envelopes and posted from Maidenhead (where Wyeth was located). The implication was that it was a policy of the Trust hospital to promote the use of minocycline which was extremely misleading.

Subsequent to this, the complainant had been accused of writing on Trust notepaper and advertising himself to general practitioners in the area for a substance which was not used locally as a first line treatment for acne. The complainant enclosed correspondence from another department of dermatology situated locally and also a copy of a letter from the director of public health.

The complainant believed that the alteration of the letter without his consent and the copying of the Trust logo on to envelopes implying that it was a Trust policy was misleading, deceptive and dishonest.

In writing to Wyeth, attention was drawn to the requirements of Clauses 2, 9.1 and 15.2 of the Code.

RESPONSE

Wyeth said that in January, 1996, the national press reported publication of a paper in the British Medical Journal (BMJ) about certain side effects associated with the use of minocycline in the treatment of acne. Although the BMJ paper discussed side effects which were well known and contained no new information, the high profile accorded to it in the lay press inevitably resulted in raised levels of concern among patients taking the product. Wyeth's view, shared by a substantial body of medical opinion, was at that time and remained that minocycline was a safe and extremely effective treatment for acne when used in accordance with its recommendations. However, there was no doubt that general practitioners felt under pressure to discontinue minocycline therapy, a trend which, had it become widespread, would have resulted in many more specialist referrals as GPs switched their patients to less effective treatments. It was therefore in the interests of both Wyeth and consultant dermatologists to encourage a more measured risk benefit assessment of minocycline within general practice.

In discussion with members of Wyeth's staff, a number of consultant dermatologists recognised the need to communicate their clinical assessment of minocycline to the medical community in which they practised. Some of them, including the complainant, committed their views to writing and Wyeth undertook to arrange for the reproduction and distribution of their letters within the

relevant locality. Wyeth emphasised that it had played no part in the drafting of the letters, which in each case reflected the individual specialist's personal opinion.

To reprint the complainant's letter to an acceptable standard it was necessary to typeset the letter and re-create the letterhead and logo on computer in order for the letter to be printed on a lithographic printing press. Colour letterheads did not scan well and scanning the complainant's typed letter for print reproduction would have produced an unacceptable result. Therefore, the typesetter used another consultant's letter as a template for the complainant's letter. In error, the heading and date of the template letter were not changed, and were thus transposed on to the complainant's letter. This error escaped the copy checking of both typesetter and her manager. As such, it was a genuine typographical error for which Wyeth was fully responsible and for which it had already apologised to the complainant. At that time he accepted Wyeth's explanation and apology.

Regarding the use of the Trust logo, Wyeth's normal practice would be to seek the Trust's consent before using the logo in this way. This practice was not followed in this case and Wyeth accepted that the Trust's logo should not have been used without the Trust's consent. Having said that, the Trust logo was of course already on the letterhead supplied by the complainant and Wyeth failed to see that the use of the logo on the envelopes, as opposed to on the letters only, added materially to the impact of the communication.

The complainant believed that the alteration of his letter invited the interpretation that it was inconsistent with local prescribing policy and that, taken together with the use of the logo on the envelopes, Trust endorsement for this position was implied. This was of course a matter for subjective judgement but Wyeth questioned whether this was in fact the result. In any case, Wyeth emphasised that it was absolutely not its intention to mislead or deceive and that there was certainly no dishonest intent involved.

The complainant also alleged that his letter was circulated beyond his immediate catchment population. This was not correct. The complainant's letter was posted only to the GP surgeries in the surrounding area to the hospital. The territory areas were marked on a map which Wyeth supplied to the Authority and a list of the GPs to whom the letter was posted was also supplied. The letters were posted from Wyeth's office in Maidenhead, hence the Maidenhead postmark.

Wyeth said that it was important to provide a comprehensive response to the matters raised by the complainant. However, these could only be considered under the Code if the reproduction and distribution of the letter constituted "promotion" as defined in Clause 1. The rationale for the exercise was fully explained above and Wyeth submitted that it was not promotional.

Wyeth made the following comments in respect of the clauses in the Code to which the Authority had referred. With regard to Clause 2, Wyeth was aware that this covered the most serious breaches but while Wyeth readily accepted that errors had been made, it submitted that these were not of a kind which would bring discredit upon, or reduce confidence in, the industry. Furthermore, with regard to Clause 15.2, none of the matters complained of originated with the medical representative who spoke with the complainant and there was no suggestion that the representative's conduct was other than in accordance with the Code.

It was clear that Wyeth had caused offence to the complainant and as Wyeth did not dispute that errors were made, it would be for the Panel to decide whether these errors constituted a breach of Clause 9.1.

PANEL RULING

The Panel considered that the fact that the letter had been reproduced and posted at Wyeth's expense and that it concerned one of the company's products meant that it had to be regarded as promotional material subject to the Code. All the requirements of the Code, such as the need for prescribing information and certification, applied to the mailing. The situation was not dissimilar to that in a previous case in which it had been so ruled (Case AUTH/320/7/95).

It was apparent that the complainant knew that some circulation of the letter was to take place as the complainant said that the "...letter had been circulated more widely than our immediate catchment population...." and the letter the complainant had provided to Wyeth was headed "Dear Colleague". Wyeth had provided a list of the doctors to whom the letters had been sent and a map showing the areas in which they were located. The Panel had no way of knowing whether the areas marked or the doctors listed were in fact those in the catchment area concerned but did not consider that this information was necessary in order to deal with the complaint.

The Panel considered that the company had behaved unacceptably. Altering the title of the complainant's letter in a way which totally changed its meaning was a serious matter whether it was the result of a "typographical error" or not. Anyone taking it upon themselves to reproduce a letter in the manner which had been adopted needed to have a high standard of checking. The copying of the Trust logo without the consent of the Trust was also a serious matter. It was perhaps understandable to some extent in relation to the letter, as the letter which was purportedly being reproduced bore the logo. It was inexcusable to reproduce the Trust logo on the outside of the envelope in which the letter would be dispatched, a tactic likely to ensure that it received prompt attention by recipients. High standards had not been maintained and a breach of Clause 9.1 of the Code was ruled.

The use of the envelope bearing the logo amounted to disguised promotion and a breach of Clause 10.1 of the Code was ruled. The fact that Wyeth's role in the distribution would not be known to recipients also breached Clause 10.1.

In addition, the Panel considered that the circumstances were such as to amount to a breach of Clause 2 as they brought discredit upon the industry and ruled accordingly.

The Panel accepted the company's contention that no blame attached to the representative concerned and therefore ruled that there had been no breach of Clause 15.2.

APPEAL BY WYETH

Wyeth accepted that it had failed to maintain the high standards required of it and that it was in breach of Clauses 9.1 and 10.1 but appealed against the ruling in respect of Clause 2. The reasons for its appeal were as follows:

1 In the Panel's ruling, "typographical error" appeared in quotation marks. Wyeth inferred from this that the Panel concluded that the miscopying of the letter was other than a genuine error. Wyeth had already made its position clear that there was no intent to mislead and, in the absence of evidence to the contrary, Wyeth submitted that the Panel should have concluded that this was a simple mistake, albeit a careless one.

2 The two breaches identified by the Panel, that was to say the mis-copying of the letter and the reproduction of the Trust's logo on the envelope, related to the manner in which the letter and its distribution were handled rather than the exercise as a whole. Wyeth submitted that the ruling of a breach of Clause 2 in these circumstances was disproportionate and therefore excessive.

APPEAL BOARD RULING

The Appeal Board noted that the complainant must have been aware that some circulation of his letter was to take place but considered that the manner in which it had been done was quite unacceptable. The fact that the title of the complainant's letter had been altered in a way which completely changed its meaning was a serious matter and represented a failure to show the high standard of care which was needed in such circumstances. The copying of the Trust's logo without consent, particularly on the outside of the envelope used to post the letter, was also a serious matter. The Appeal Board upheld the Panel's ruling that there had been a breach of Clause 2 of the Code.

The appeal therefore failed.

Complaint received **3 January 1997**

Case completed **21 March 1997**

Case AUTH/492/1/97

YAMANOUCHI v LOREX SYNTHÉLABO

Promotion of Xatral

Yamanouchi complained about the promotion of Xatral by Lorex Synthélabo.

The Panel ruled no breach of the Code with regard to an allegation that claims relating to use of the terms "uroselective", "clinical uroselectivity" and "uroselective and effective" were misleading, all embracing and had not been substantiated to Yamanouchi on request. The Panel ruled a breach as it considered that eyeshades provided to doctors as a promotional aid were not relevant to the practice of medicine. No breach of the Code was ruled with regard to a wrapper advertisement alleged to fail to state where the prescribing information could be found. A claim "To avoid close encounters of the BPH kind" was ruled in breach as it implied the product would work in 100% of patients and this was not so. A statement that Xatral did not require initial dose titration was not considered to be promotion outside the licence and no breach was ruled.

Yamanouchi Pharma Ltd complained about the promotion of Xatral (alfuzosin) by Lorex Synthélabo Limited. There were a number of allegations concerning a number of different promotional items. The promotional items at issue were:

1 GP detail aid (XAT.GP.DET3 January 1996)

2 GP mailing consisting of a "Dear Doctor" letter and a leaflet (XATGA(L)/May 1996)

3 Journal advertisement (XAT.BO2). The advertisement provided by Lorex Synthélabo bore the reference XSR/AD-HA October 1996 which was the master for XAT.BO2

4 GP mailing consisting of a "Dear Doctor" letter (Ref XAT104(L) and a leaflet. The leaflet provided by Lorex Synthélabo bore the reference XAT104(M) October 1996)

5 A wrapper advertisement on MIMS (XSR/W-M October 1996)

The allegations were considered as follows:

1 Use of the claims "Uroselective", "Clinical uroselectivity" and "Uroselective and effective"

COMPLAINT

Yamanouchi said that all of the promotional material claimed that Xatral was uroselective. The claim was not referenced in most of the promotional material and was not supportable. The claim implied a special merit for Xatral which was not supported by any available data. The only time a uroselective claim was referenced was in the detail aid. The two references quoted were Lefevre-Borg *et al* (1992) and Buzelin *et al* (1995 data on file) supplied to Yamanouchi by Lorex Synthélabo.

Yamanouchi pointed out that the Lefevre-Borg study compared the effects of alfuzosin, prazosin and terazosin on urethral pressure in cats and the effect of these products on the blood pressure of spontaneously hypertensive rats. The promotional material did not specify that animal data was used in this study. Buzelin *et al* compared the effect of alfuzosin and placebo in men with benign prostatic hypertrophy (BPH). The study stated "Blood pressure changes: with Xatral there was a slight (but significant) reduction in supine systolic blood pressure over the treatment period. This reached statistical significance at month 2 but had disappeared by

the end of the treatment period".

Yamanouchi alleged that the references did not support the claim and demonstrated that alfuzosin was not selective in man as there was an effect on blood pressure.

Yamanouchi said that the GP mailing dated October 1996 stated that "Xatral SR is the first uroselective alpha$_1$ blocker specifically licensed for the treatment of BPH, demonstrates clinical uroselectivity and offers....".

Yamanouchi pointed out that "clinical uroselectivity" was a term defined at a WHO International Consultation on Benign Prostatic Hyperplasia. The published proceedings stated:

"A clinically relevant definition of uroselectivity can only be made in man. It is known that effects on blood pressure in hypertensive subjects are more pronounced than normotensives. Theoretically, a drug could affect blood pressure in a hypertensive subject before it has any noticeable effects on the urethra, ie, the drug has no uroselectivity. The same drug may reduce outflow resistance in a normotensive subject without any effects on blood pressure, ie, the drug is uroselective. It is therefore necessary to have a broader definition of clinical uroselectivity, taking into account that the clinical endpoints outflow obstruction, lower urinary tract symptoms and adverse effects may be more or less independent. A suggested definition of clinical uroselectivity is "desired effects on obstruction and lower urinary tract symptoms related to adverse effects". It should be noted that clinical uroselectivity is not an all or none phenomenon".

Yamanouchi argued that the crux of the definition was that clinical uroselectivity was patient dependent ie if the medicine provided relief of BPH symptoms with no side effects, it could be clinically uroselective for that patient. It was not possible to describe any medicine as clinically uroselective as this implied an absolute that would be true for all patients which was not so. The statement would be true in some patients but not all and therefore the claim was all embracing and not appropriate.

In addition the WHO statement that "A clinically relevant definition of uroselectivity can only be made in man" invalidated and excluded the use of animal data to support the claim eg Lefevre-Borg *et al* as referenced by Lorex Synthélabo in its promotional material.

Yamanouchi referred to the clinical papers supplied by Lorex Synthélabo in support of the claim. The study by Lukacs (1996) stated that 59% of those patients who withdrew from the study following adverse events withdrew following vasodilatory related events and 7.9% of the withdrawals were due to postural hypotension. Buzelin *et al* referred to the fact that although the effects of alfuzosin on supine blood pressure were small and unlikely to be clinically significant, a statistically significant effect was seen. The table in the paper indicated that in the alfuzosin group a statistically significant greater fall in standing diastolic blood pressure occured compared to the placebo group ($p = 0.02$). From these data it was apparent that alfuzosin had a small but significant effect on blood pressure and in some patients did cause significant vasodilatory side effects.

Yamanouchi said that the term "uroselective" strongly implied that only alpha receptors in the urological tract were affected by alfuzosin; this was clearly not so. Three papers published by Synthélabo Recherche stated that alfuzosin was not selective for the alpha$_1$ subtype which predominated numerically and functionally in the human prostate. Graham *et al* said that most of the alpha$_1$ adrenoceptor antagonists currently used in the treatment of BPH such as terazosin, bunazosin, doxazosin and alfuzosin did not show *in vitro* selectivity towards any of the alpha$_1$ adrenoceptors cloned to date. Dennis *et al* said that the alpha$_{1A}$ selective antagonist, tamsulosin, was compared to the non selective antagonists alfuzosin and doxazosin. Faure *et al* said that competitive inhibition experiments revealed that the non selective alpha$_1$ subtype antagonsist alfuzosin produced a monophasic inhibition curve.

Yamanouchi alleged that claiming selectivity for the urological tract was not appropriate or supportable by any available data. Therefore use of the claims "uroselective", "clinical uroselectivity" and "uroselective and effective" were in breach of Clauses 7.2 and 7.8 of the Code. The company had not yet received adequate substantiation of the claims and therefore Lorex Synthélabo was also in breach of Clause 7.4.

RESPONSE

Lorex Synthélabo submitted that data existed to show that relative to other alpha adrenergic blockers (except tamsulosin which was marketed after Xatral) alfuzosin exhibited pharmacological and clinical selectivity for the lower urinary tract. The selectivity was not absolute, it was relative. The company had never made the claim that alfuzosin was urospecific. Lorex Synthélabo said that as well as animal data a large number of patients had been studied and the profile seen for alfuzosin was supportive of its claim. Lorex Synthélabo provided what appeared to be a review article of the area to support its submission. A copy of a confidential draft paper by Buzelin *et al*, which had been accepted for publication in the British Journal of Urology, was also provided.

Lorex Synthélabo said that the precedent for using the nomenclature (...selective) for agents which exhibited a relative selectivity for certain body organs or systems was well established in pharmacology and clinical medicine from the example of the acceptance of the use of the term "cardioselective" when applied to certain beta blockers (for example, atenolol). There was complete acceptance and understanding that cardioselective beta blockers, whilst showing selectivity for the cardiovascular system relative to the non cardioselective beta blockers, could show effects on other body systems, for example the bronchial tree, particularly in higher doses or in susceptible individuals such as asthmatics. In exactly the same way uroselective alpha adrenergic blockers (alfuzosin and tamsulosin) showed selectivity for the lower urinary tract relative to the non uroselective alpha blockers (eg prazosin and terazosin) but could show effects on other body systems, for example the cardiovascular system, in higher doses or in susceptible individuals.

The non selective alpha blockers were originally developed for the treatment of hypertension showing their non-uroselectivity, the newer agents were specifically developed for benign prostatic hypertrophy,

because of their greater selectivity. The term uroselective was also in common clinical use as witnessed by the use by over 20 consultant urologists in a newsletter sent out to general practitioners.

PANEL RULING

The Panel did not accept that the use of the term "uroselective" was unreasonable *per se*. In the Panel's view the term would be understood by GPs as meaning that the product acted predominantly, but not specifically, on one type of receptor similar to the way the term "cardioselective" was understood. The term "uroselective" was not absolute. The Panel then went on to consider whether Xatral was a uroselective product.

The Lukacs paper referred to by Yamanouchi included 13, 389 patients in two postmarketing studies. No comparative medicine was studied. 89.7% of patients completed the treatment period. Drop outs were recorded in 10.3% of patients. The drop out rate due to intolerance was low (3.7%). Two thirds of the adverse events leading to discontinuation were vasodilatory and occurred in 2.7% of the patients. 0.42% of the overall population dropped out due to postural hypotension. The patients who dropped out for intolerance were statistically significantly older than those of the reference population. The paper stated that in the pivotal controlled study for the product, the drop outs for intolerance were 10.8% of patients treated with alfuzosin with the percentage of drop outs in the placebo group being quite similar (9%). The lower incidence might be due to the reporting only of the clinically significant events in a general practice based trial as opposed to spontaneous reporting in phase III trials.

The Buzelin study (data on file) assessed the efficacy and safety of a 5mg sustained release formulation of alfuzosin. It was stated that "Blood pressure changes: with Xatral SR there was a slight (but significant) reduction in supine systolic blood pressure over the treatment period" (3 months) "This reached statistical significance at month 2 but had disappeared by the end of the treatment period. Absolute changes seen were small and unlikely to be of clinical relevance.

The Panel noted the studies referred to by Yamanouchi. The Dennis *et al* paper referred to alfuzosin being a non selective antagonist with reference to tamsulosin being an $alpha_{1A}$ selective antagonist which was a further sub division of $alpha_1$ antagonists. It appeared to the Panel that Faure *et al* was similarly referring to an $alpha_1$ sub type antagonist and not an $alpha_1$ agonist.

It appeared from the correspondence between the companies prior to the complaint being made to the Authority, that the companies had agreed that the affinity of alfuzosin for the $alpha_1$ receptor was 40-60 times greater than its affinity for $alpha_2$ receptors (Bourin).

The Panel noted that the entry for Xatral in the ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996/97 stated that *in vitro* pharmacology studies had documented the specificity of alfuzosin for the alpha one adrenoceptors located in the trigone of the urinary bladder, urethra and prostate. In vivo animal studies had shown that alfuzosin reduced urethral pressure and therefore the resistance to urinary flow. The data sheet stated that alfuzosin might cause moderate antihypertensive effects.

The Panel examined the references provided by Lorex Synthélabo to support the claims. The Panel noted that certain of the material, the draft paper awaiting publication and the newsletter could not be sent to Yamanouchi and were therefore not taken into account by the Panel during its consideration. The Panel noted that the references provided by Lorex Synthélabo did refer to alfuzosin as a selective $alpha_1$ adrenoceptor antagonist.

The Panel considered that the term "uroselective" with reference to Xatral was justified. In the Panel's view the intended audience would understand the term to mean that the product had demonstrated relative (and not absolute) selectivity for alpha receptors in the lower urinary tract.

The Panel did not consider that the claims "uroselective", "Clinical uroselectivity" or "uroselective and effective" in relation to Xatral were misleading or all embracing. The Panel ruled no breach of Clauses 7.2 and 7.8 of the Code. The Panel ruled no breach of Clause 7.4 of the Code in that Lorex Synthélabo had provided Yamanouchi with material to substantiate the claims.

2 Gift of eye shades for doctors

This allegation concerned the GP mailing May 1996 which consisted of a "Dear Doctor" letter and a leaflet. The theme of the leaflet was "Women Suffer from BPH Too" and a pair of pink eye shades was attached to one of the pages of the leaflet.

COMPLAINT

Yamanouchi alleged that the gift of eye shades was not relevant to the practice of medicine in breach of Clause 18.2 of the Code.

RESPONSE

Lorex Synthélabo said that when asking a number of general practitioners and hospital physicians for suggestions for low cost gifts relevant to the practice of medicine, a suggestion was made that eye shades could be provided. Many doctors now had a morning off after a busy night on call and the provision of eye shades would help them to catch up on missed sleep during daylight hours. Also many doctors travelled extensively for medical conferences with widespread air travel. Provision of eye shades could facilitate the ability to sleep whilst travelling. The eye shades cost 53 pence each.

Lorex Synthélabo pointed out that the promotion was completed many months ago and was no longer in use.

PANEL RULING

The Panel noted that the eye shades were within the requirements of the Code as far as cost was concerned. The Panel did not accept, however, that the eye shades were relevant to the practice of medicine. The Panel therefore ruled a breach of Clause 18.1 of the Code.

3 Provision of prescribing information

This allegation concerned the wrapper advertisement which appeared as a wrapper round MIMS, January 1997.

COMPLAINT

Yamanouchi said that the advertisement was a full advertisement which appeared not to carry the prescribing information. The fact that the prescribing information was on the reverse of the wrapper was discovered after tearing the wrapper down the gummed seal. No reference was made on the advertisement to the fact that prescribing information could be found on the reverse side of the wrapper. A breach of Clause 4.5 was alleged.

RESPONSE

Lorex Synthélabo pointed out that the prescribing information was available on the wrapper. It accepted however that no reference was made in the advertisement to its appearance overleaf and whilst the company believed that all prescribers opening the wrapper would have seen the prescribing information, it accepted that Clause 4.5 of the Code had been breached. The material was no longer in use.

PANEL RULING

The Panel noted that Clause 4.5 of the Code referred to journal advertising where the prescribing information appeared over the page. The Panel did not consider that the wrapper was a journal advertisement subject to Clause 4.5. In the Panel's view, the wrapper was a loose outsert and needed to comply with Clause 6.3. No breach of Clause 4.5 was ruled.

In order to comply with Clause 6.3, the wrapper should not have a greater surface area than the page size of the journal, printed on one or both sides. There was no need to indicate where the prescribing information could be found. The wrapper at issue was too large in that the total surface area was in excess of the surface area of one page of MIMS. There had been no allegation in this regard and the Panel did not therefore make a ruling. The Panel requested, however, that Lorex Synthélabo be advised of its views.

4 Claim "To avoid close encounters of the BPH kind"

This claim appeared on the wrapper for MIMS and in the journal advertisement.

COMPLAINT

Yamanouchi alleged that the claim was not in common medical usage and raised the question of what was a "close encounter of the BPH kind". Yamanouchi alleged that the claim implied that Xatral could be used prophylactically to prevent the development of BPH. This was outside the product licence which was for the "symptomatic relief of benign prostatic hypertrophy". In addition, the use of the word "avoid" made the claim an absolute implying that Xatral worked in 100% of patients. This was all embracing and could not be substantiated. Breaches of Clauses 3.2, 7.3, 7.4 and 7.8 were alleged.

RESPONSE

Lorex Synthélabo said that the claim "To avoid close encounters of the BPH kind" was a clear reference to the treatment of the symptoms (close encounters) suffered by patients with BPH and was in line with the data sheet. The visual associated with the slogan was a picture of a man at night in pyjamas making the association with nocturia, one of the major symptoms of BPH. Lorex Synthélabo said that it had not implied that it was trying to avoid BPH. The use of the phrase "to avoid" did not make the claim absolute. The company had never claimed or implied Xatral worked in 100% of patients, although the majority of patients treated would have a reduction in the symptoms of BPH and an improvement in quality of life. The phrase "to avoid" in everyday usage might infer that one was trying to combat, in this case, the symptoms of BPH (the goal of therapy with Xatral) but did not say that one would succeed.

The claim was not all encompassing, it had been substantiated and appropriate supporting documents provided to Yamanouchi.

PANEL RULING

The Panel did not consider that the claim implied that Xatral could be used prophylactically. The claim referred to the symptomatic control of BPH. The Panel ruled no breach of Clause 3.2 of the Code.

The Panel considered that the use of the phrase "to avoid" implied that the product would work in 100% of patients and this was not so. The claim was misleading, all embracing and not capable of substantiation. Breaches of Clauses 7.2, 7.3 and 7.8 were ruled.

5 Initial dose titration

This allegation concerned the GP mailing dated October 1996. The "Dear Doctor" letter had a PS at the bottom "Xatral SR does not require initial dose titration".

COMPLAINT

Yamanouchi said that the ABPI Compendium entry for Xatral stated "Elderly and treated hypertensive patients: As a systematic precaution, the initial dose should be one tablet Xatral 2.5mg in the morning and one tablet Xatral 2.5mg in the evening. If additional efficacy is required, and Xatral is well tolerated, the patient may then be given one tablet Xatral SR 5mg twice daily."

Yamanouchi said that the data sheet clearly stated that dose titration was necessary for some groups of patients. In view of the recommendations regarding elderly patients and patients with renal and hepatic insufficiency, the statement that initial dose titration was not required contradicted the data sheet and was irresponsible as it could put some patients at risk. The claim was therefore outside the dosing regimen in breach of Clause 3.2 of the Code. In view of the potential risk to some patients if this claim were to be followed by a prescribing physician, a breach of Clause 2 of the Code was also alleged.

RESPONSE

Lorex Synthélabo submitted that dose titration was a term

used when dosage was started at subtherapeutic levels in order to ensure that an initial dosage was tolerated. If this initial dose was tolerated, then the dosage was titrated upwards in steps until an efficacious and tolerated dose was achieved. Because of the antihypertensive effects of the original alpha blockers, dose titration was essential to avoid initial dose hypotension with significant risk to the patient.

This situation was entirely different for products which had a range of efficacious doses. Clinically a lower but efficacious dose might be used initially particularly in special subgroups. If additional efficacy was required (only likely in a proportion of cases) this was acheived by moving up the dose range. A vast array of products fitted into this category for example, beta blockers, calcium antagonists. Xatral belonged to this category. The critical issue was that the dose being used initially was efficacious and might well be all that was necessary to achieve the desired effect.

PANEL RULING

The Panel accepted Lorex Synthélabo's definition of dose titration whereby dosage was started at subtherapeutic levels in order to ensure that the initial dose was tolerated. The initial dose of Xatral in the elderly could be sufficient to achieve the desired effect. The Panel did not accept that the company was promoting outside its licence and therefore ruled no breach of Clauses 3.2 and 2 of the Code.

Complaint received 29 January 1997

Case completed 30 April 1997

CASE AUTH/493/1/97

CLINICIAN v SERONO

Curosurf mailing

A clinician made a number of complaints about a Curosurf mailing issued by Serono.

In relation to the use of the word "natural" to describe the product, the Panel noted that Curosurf was derived from porcine lung and that by common usage such a surfactant would be described as "natural" as opposed to "synthetic". The data sheet for Curosurf described it as a natural surfactant. The Panel did not consider that the intended audience would be misled by the brochure as it would be familiar with the description of surfactants as either synthetic or natural. The brochure clearly stated the source. No breach of the Code was ruled. On appeal by the complainant, the Appeal Board's view was that "natural" did not mean the "same as human". The Appeal Board agreed with the Panel and upheld the Panel's ruling of no breach of the Code.

The Panel considered that a statement referring to a meta analysis of treatments with natural surfactants compared with synthetic surfactants would imply that more than one synthetic surfactant had been examined. This was not the case and the use of the plural was ruled to be misleading in breach of the Code.

The Panel considered that the way in which data from two separate trials had been presented was misleading as it implied that it was from a direct comparison of Curosurf and a synthetic surfactant. In addition the data had been used to support a claim for a lower incidence of complications in Curosurf treated infants. There was, however, only a lower incidence of one complication, although subsequent studies did not support this finding. The Panel considered that the data did not represent an up to date evaluation of all the evidence and its use as the basis of a claim was in breach of the Code.

The Panel noted that the graph relating to the data above was labelled "Curosurf" and "synthetic surfactant". The Panel considered that this implied that the results shown might hold true for Curosurf versus any synthetic comparator. The synthetic comparator in question had been Exosurf and the graph should have been labelled with its generic name. The Panel ruled that the labelling of the graph was misleading in breach of the Code.

A clinician at a neonatal intensive care unit complained about the promotion of Curosurf by Serono Laboratories (UK) Ltd. The item in question was a mailing consisting of a four page brochure (C0400796) and a covering "Dear Doctor/Nurse" letter. It had been sent primarily to consultant paediatricians. The title of the brochure was "*Our* experience comes *naturally*". There were a number of allegations about the brochure which were considered as follows:

1 Use of the word "natural"

COMPLAINT

Curosurf was referred to as a natural surfactant. The complainant appreciated that this was how it was referred to in the data sheet. However, Curosurf was not natural in any real sense of the word. It was a highly modified extract of minced pig lungs that contained only some of the lipids that were normally present in surfactant. Those present were not in the same proportions as in human surfactant. It also contained two apoproteins of the four apoproteins present in normal surfactant and the two proteins present were not present in the same proportions as they occured in normal surfactant. By applying the term "natural" it suggested that it was identical to natural human surfactant. The complainant alleged that this was misleading clinicians into thinking this surfactant was exactly as it occurred in the natural state. An honest description would be animal extracted (or derived) surfactant.

RESPONSE

Serono submitted that as part of a recognised classification, surfactants used in respiratory distress syndrome (RDS) were divided into two categories, natural

or synthetic. This classification was in common usage by all the leading neonatologists who presented on surfactant therapy. Modified natural surfactant was defined by Martindale as "bovine or porcine lung extract to which synthetic surfactants are added". Curosurf was poractant alfa which was a British Approved Name for an "extract of porcine lung containing not less than 90% of phospholipids, about 1% of hydrophobic proteins (SP - B and SP - C), and about 9% of other lipids". Curosurf contained no synthetic detergents or spreading agents and had, therefore, been described as "natural surfactant".

Synthetic or semi-synthetic surfactants often contained, in conjunction with phospholipids, artificial agents like hexadecanol and tyloxapol and synthetic phosphatidlyglycerol which aided spreading.

Serono fully agreed that Curosurf did not contain the same lipid fractions as human surfactant. In the human, the different lipid fractions were produced at different stages of gestation, so it was not possible to describe the proportions of the lipids at the time of pre-term birth or therapy with surfactant. Serono had never claimed that Curosurf was the same as human surfactant.

Finally, the very first sentence of the brochure reiterated the fact that Curosurf was derived from porcine lung and had similarities with human surfactant, in that it contained most of the major constituents found in human surfactant.

PANEL RULING

The Panel noted that the brochure was entitled *"Our* experience comes *naturally"* and that "the natural approach" was used in all three headlines inside the piece. The Panel noted that the first paragraph of text on page two of the brochure stated that Curosurf was derived from porcine lung and had many similarities with human surfactant. It was thus made clear that Curosurf was not the same as human surfactant. The back page of the brochure, which contained the prescribing information, had the stab point "Natural, low volume, rapid acting surfactant".

The Panel noted that, by common usage, surfactants were divided into only two categories - natural or synthetic - and that the data sheet for Curosurf described it as a natural surfactant.

The Panel had some sympathy with the complainant and considered that there might have been some overplay on the word "natural". The Panel did not consider, however, that the intended audience would be misled by the brochure as it would be familiar with the description of surfactants as either synthetic or natural.

The brochure had clearly stated the source of Curosurf. The Panel did not consider that it was misleading in this regard. No breach of Clause 7.2 of the Code was ruled.

APPEAL BY COMPLAINANT

The complainant appreciated the thoughtful comments of the Panel in the matter that the term "natural surfactant" was in common usage. However, if the complainant had understood the information correctly it was agreed by Serono and the Panel that Curosurf was not truly natural. The complainant suggested that even though this term was in common usage, the term was not accurate and that to allow it to continue to be used in this way perpetuated the inaccuracy.

RESPONSE FROM SERONO

Serono said it strongly disagreed with the complainant's comments on the use of the term "natural". Firstly, the complainant appeared to be wrongly interpreting the term "natural" to mean "of human origin" and this led the complainant to misunderstand Serono's response. Curosurf was truly natural under the standard and accepted nomenclature for this group of products. Serono had never claimed that Curosurf was the same as human surfactant.

Serono submitted that Professor Halliday, a world expert in surfactant therapy, defined the standard nomenclature for exogenous surfactants stating that natural surfactants were those which had been prepared from animal lungs either by lavage or mincing before extracting the phospholipids and surfactant proteins B and C. Professor Halliday included Curosurf in that group, along with a number of other animal-derived surfactants. Professor Halliday differentiated these from synthetic exogenous surfactants by defining the latter as ".... those prepared from DPPC and other agents to facilitate adsorption and spreading". In this group he included products like Alec (pumactant), marketed through Britannia Pharmaceuticals and Exosurf (colfosceril palmitate) marketed by Glaxo Wellcome.

Serono said that Professor Halliday was one among many world experts to use this standard nomenclature. Serono enclosed references from a number of journals, clearly stating "natural" as the description of various animal-derived surfactant preparations. Serono pointed out that not referring to Curosurf as a natural surfactant would be more misleading to the health professionals, as they might interpret the change from the standard nomenclature to represent a change to the product or even view it as a new product altogether.

Serono said that if the complainant continued to challenge the standard classification then it might respectfully request that the complainant took this up with the professionals and professional bodies that had formulated the term and been using it for nearly 20 years, rather than pursue a pharmaceutical company that purely adopted the recognised standard.

FURTHER COMMENTS FROM THE COMPLAINANT

The complainant said that despite Serono's legitimate comment that the word "natural" had been applied to surfactant for a number of years and in many respected papers, this word was really used as a short hand title to differentiate the animal derived surfactants from artificial surfactant. These papers were not written with a view to careful definition and in particular not written with the careful dedication to accuracy of description which was beholden on the pharmaceutical company.

The Collins English Dictionary defined natural as "existing in or produced by nature", "as is normal or to be expected".

The complainant contended that Curosurf was derived

from animal lungs but no longer had the composition of the surfactant as it occurred in the lungs. Its lipid and protein composition were different to surfactant analysed after being extracted directly from lungs. It was therefore not as nature made it or intended it. It had been artificially changed from the natural state.

The complainant said that the other animal derived surfactant marketed in the UK was Survanta. In the data sheet this was not referred to as a natural surfactant, it was called a "bovine lung extract". This was a more accurate description of the product.

The complainant was concerned that products should be accurately described and advertised. To call Curosurf natural was not an accurate description and to advertise it with the description of natural was misleading people into thinking that it was as made in nature.

The complainant pointed out that insulins were medicines which could have been described as natural as they were an extract of the natural insulin. The word natural did not occur in the data sheet related to insulins or in their advertising literature. For example, Hypurin was described as "a highly purified bovine insulin".

The complainant said that using the word natural to describe a surfactant was an inappropriate and misleading description.

APPEAL BOARD RULING

The Appeal Board noted that the product data sheet described Curosurf as "a natural surfactant". In the Appeal Board's view the term "natural" implied that Curosurf was derived from either a plant or animal source as opposed to being synthetic. The Appeal Board did not consider that, in this context, "natural" meant "the same as human".

The Appeal Board agreed with the Panel. The intended audience would not be misled by the brochure as it would be familiar with the description of surfactants as either synthetic or natural. The brochure clearly stated the source of Curosurf. It was not misleading in this regard. The Appeal Board upheld the Panel's ruling of no breach of Clause 7.2 of the Code.

The appeal on this point therefore failed.

The other allegations all referred to page three of the brochure which was headed "The clinical benefits of the natural approach". Certain conclusions from a meta analysis, relating to infant survival and the incidence of airleaks, were given in the first paragraph followed by a second paragraph of data from another study together with a graph from that study.

2 Use of the term "synthetic surfactants"

COMPLAINT

The complainant referred to the first paragraph on the page in question which stated:

"Halliday has shown by meta analysis that treatment with natural surfactants results in 1 more survivor for every 42 infants treated, 1 fewer airleak for every 14 infants treated and 1 more survivor with healthy lungs for every 25 infants treated compared with synthetic surfactants".

The complainant said that "compared with synthetic surfactants" was misleading by the use of the plural as the comparison had only been with one synthetic surfactant ie Exosurf. This was not a comparison with any other synthetic surfactant.

RESPONSE

Serono submitted that this sentence was a direct quote from the most recent paper from a world opinion leader in surfactant therapy, hence the use of the plural "surfactants". However, there was some data available on another synthetic surfactant, Alec, which showed that it did not reduce the incidence of air leaks when given as prophylaxis compared to placebo; 17% and 26% of neonates developed air leaks with Alec vs 20% and 30% with placebo. These differences were not significant in either study and furthermore the authors quoted "Artificial surfactant had no effect on the incidence of pnemothoraces, pulmonary interstitial emphysema, ...". However, Curosurf significantly reduced the incidence of air leak complications when given as rescue treatment or prophylaxis. In rescue treatment, pneumothorax occurred in 7-19% Curosurf treated neonates vs 36% controls ($p<0.05$); pulmonary interstitial emphysema in 1-23% following Curosurf vs 39% in the control group ($p<0.05$). When Curosurf was given as prophylaxis, the incidence of pnemothorax was 7% (vs 9% in controls; NS) and pulmonary intestinal emphysema 7% (vs 14% in controls; $p<0.05$).

Mortality rates with Alec as prophylaxis were reported as 9% vs 15% controls (NS) and 14% vs 27% controls ($P<0.002$). It was not appropriate to compare the number of extra survivors per number of patients treated, reported in these articles, with those mentioned in the brochure as the indication for treatment was different; some 25% (37/149) of those included in the Alec study (control group) did not go on to develop respiratory distress syndrome and would therefore not have been entered into the Curosurf treatment studies.

PANEL RULING

The Panel noted that the reference cited (Halliday 1996) was a review article entitled "Natural vs Synthetic Surfactants in Neonatal Respiratory Distress Syndrome". The Panel could not find the sentence said by Serono to be a direct quote from the paper. It appeared to the Panel that the sentence was based on the Halliday review but was not a direct quote. Halliday reviewed nine trials each of which compared one natural surfactant with one synthetic surfactant. In every trial Exosurf was the synthetic comparator while the natural surfactant was beractant (Survanta) in seven of the trials and calf lung surfactant extract (CLSE; Infasurf) in the other two studies reviewed. A comparative trial of Curosurf and Exosurf was not reported.

The Panel considered that the statement "Halliday has shown by meta analysis that treatment with natural surfactants .... compared with synthetic surfactants", would be taken by most readers to imply that more than one synthetic surfactant had been examined. This was not the case. The Panel considered that the statement was

misleading as alleged and ruled a breach of Clause 7.2 of the Code.

3 Use of the Rollins data

COMPLAINT

The complainant said that in the second paragraph Serono had quoted from a paper (Rollins *et al* 1993) which had compared the results between Curosurf and a synthetic surfactant. This was an inappropriate and a very unsatisfactory paper for a reputable pharmaceutical company to quote showing the benefits of its product. This paper was not a randomised comparison of Curosurf v Exosurf. It reported the historical comparison in two hospitals where Exosurf was used initially and then changed to Curosurf. There were 45 patients treated with Exosurf and 21 treated with Curosurf. The Curosurf babies were of older gestational age (32.1 weeks, compared with 30.6 weeks), larger size (1841g compared with 1616g) and a higher proportion had been treated with antenatal steroid (43% compared with 16%). They were bound to have had a better outcome than the babies treated with Exosurf. Quoting this paper was misleading in favour of Curosurf and either showed ignorance of the way the study was done or was frankly dishonest.

The complainant referred to the end of the paragraph describing the Rollins paper which stated that there were fewer complications in Curosurf treated patients. The complainant said that it was misleading because there was a reduction in only one complication, intraventricular haemorrhage. In addition it was misleading for Serono to suggest that Curosurf reduced brain haemorrhages compared with Exosurf when this had not been shown by any of the well conducted randomised controlled trials.

RESPONSE

Serono said that the Rollins paper was published in The Journal of Perinatal Medicine, which was a fully refereed journal. The paper clearly stated that it was retrospective and Serono had stated that in its discussion of the paper's conclusions. In addition, Serono considered that its brochure was explicit concerning the numbers in the groups.

Serono said that what this study did show was that there was no significant difference between the Exosurf and Curosurf treated groups, based on birthweight (1616g vs 1841g: NS), gestation (30.6 wks vs 32.1 wks; NS) or steroid usage (16% vs 43%; NS). Serono accepted that steroids had an impact, but this could well have been countered by the mode of delivery, in that more of the Curosurf babies were born by caesarean section (67% vs 51% Exosurf) which in itself carried a higher instance of respiratory problems.

With regard to the use of the term "complication" as opposed to "complications". Serono submitted that the complications being described were those of intraventricular haemorrhage (IVH) and the company had used the plural to discuss the instances of IVH.

What was clear was that less IVH occurred in those treated with Curosurf in this particular report. However, the conclusion Serono was drawing, and representing graphically, was based on time spent in oxygen.

Serono agreed with the complainant's point that a randomised controlled trial looking at the incidence of complications would be most useful. Unfortunately, at the present time this was the only published work looking at Curosurf and Exosurf and must, therefore, stand until overtaken by any new work.

Serono said that there was not a consistent message from other studies with either Curosurf or Exosurf in the incidence of IVH reported; it was furthermore difficult to interpret these reported data as these figures might not be directly comparable (eg major cerebral abnormalities vs all grades of IVH). What was important from the Rollins report was that this was a true representation of clinical practice where the same nursing teams were involved in both trials and was devoid of multicentre bias.

PANEL RULING

The Panel noted that the Rollins (1993) paper was not a direct comparison of Curosurf and Exosurf. It was a retrospective analysis of two groups of infants who had been treated at the same hospital but as part of two separate large multicentre trials the OSIRIS trial and the Curosurf 4 trial. The two groups were, therefore, small sub groups from two much larger trials. This point was not explained in the mailing. The Panel considered that readers would assume that the two groups were from the same study which was not the case. The Panel accepted that statistically the two groups were well matched in terms of birthweight, gestational age etc but questioned whether some of the differences between the two groups were sufficient to make a clinical difference.

The Panel noted that the data from Rollins was used to claim that, compared to a synthetic surfactant, Curosurf treated infants spent less time on oxygen. The data from the two groups was shown on a single bar chart with the bars representing Curosurf overlapping those representing the synthetic surfactant. The Panel considered that visually this graph reinforced the impression that the results were all from one trial when this was not so. In addition the data was used to claim that, compared to a synthetic surfactant, there was a lower incidence of complications in Curosurf treated infants. There was, however, only a lower incidence of intraventricular haemorrhage (IVH), all other complications observed occurred with a similar incidence in both groups. The Panel noted, however, that papers published after the Rollins paper did not support the claim for Curosurf of a lower incidence of IVH but instead showed that the choice of surfactant had little if any impact in this regard. The Panel considered that the Rollins paper did not represent the current balance of evidence with regard to the incidence of IVH with Curosurf.

The Panel considered that the Rollins data was not sufficiently robust to be used as the basis of major claims for Curosurf. The way in which the data had been presented, as noted above, was misleading and so the Panel ruled a breach of Clause 7.2 of the Code. In addition the data regarding IVH was not based on an up to date evaluation of all the evidence and so the Panel ruled a breach of Clause 7.2.

4 Synthetic surfactant data not attributed specifically to Exosurf

COMPLAINT

The complainant noted that the graph accompanying the description of the Rollins paper was annotated "Curosurf" and "synthetic surfactant". The latter was in fact Exosurf. The complainant considered that the comparative surfactant should have been labelled as Exosurf to ensure that the reader did not misascribe the data to any other synthetic surfactant.

RESPONSE

Serono submitted that under the Code other companies' trade names could not be used without prior permission.

PANEL RULING

The Panel noted that Clause 7.10 of the Code stated that "Brand names of other companies must not be used unless prior consent of the proprietors has been obtained". This Clause did not prohibit companies using the generic name of competitor products in promotional material.

The Panel noted that the synthetic surfactant featured in the Rollins paper was Exosurf. To refer to a "synthetic surfactant" might give the impression that, as a comparator to Curosurf, the specific surfactant used was not important only that it was synthetic. The Panel considered that readers might assume that the results reported by Rollins held true for Curosurf versus any synthetic surfactant comparator. In the Panel's view the generic name for Exosurf should have been used and considered that not to have done so in these circumstances was misleading. A breach of Clause 7.2 was ruled.

Complaint received **29 January 1997**

Case completed **28 May 1997**

CASE AUTH/498/2/97 *NO BREACH OF THE CODE*

CONSULTANT PSYCHIATRIST v BRISTOL-MYERS SQUIBB

Sponsored self help booklet

A consultant pyschiatrist alleged that a booklet, produced by a self help group and supported by Bristol-Myers Squibb, was a subtle advertisement for Dutonin.

The Panel noted that the booklet, which gave patients information on how depression and its treatment might affect their sex lives, did not mention any specific antidepressant by either generic name or brand name. The Panel considered that the booklet might encourage patients to consult their GPs if they were experiencing sexual problems and to request a prescription for "one of the newer antidepressants" as referred to in the booklet but the booklet did not encourage patients to ask for a specific antidepressant. There were antidepressants other than Dutonin which were also "newer". No breach of the Code was ruled.

COMPLAINT

A consultant psychiatrist complained about a booklet entitled "Depression & your sex life" produced by the self help group, Depression Alliance.

The bottom of page six of the booklet posed the question "Are sexual side effects common with all antidepressants?" with the reply "No. One of the newer antidepressants is less likely to cause the sexual side effects that you may experience with TCAs and SSRIs".

The back outside cover of the booklet stated that Depression Alliance was supported by Bristol-Myers Squibb Pharmaceuticals. The complainant pointed out that the company manufactured Dutonin, a new antidepressant which was being promoted in advertisements and by the company's representatives as having a very low rate of sexual side effects.

In the covering letter sent with the booklet, the Depression Alliance stated that the intention was to distribute it widely in general practice and other settings.

The complainant wholeheartedly approved of providing patients with as much information as possible about their illnesses, the treatment and the side effects of treatment. However, in his opinion, this booklet overstepped the dividing line between what was patient information and what was promotion of a particular product. The complainant alleged that the booklet was a subtle advertisement for Dutonin.

In responding to the complaint, Bristol-Myers Squibb Pharmaceuticals Limited was asked by the Authority to consider Clauses 20.1 and 20.2 of the Code.

RESPONSE

Bristol-Myers Squibb submitted that the production of the booklet was financially supported by the company at the request of Depression Alliance. It was certified within the company to ensure compliance with the Code. Distribution of the booklet to general practitioners and psychiatrists was undertaken by Depression Alliance.

Bristol-Myers Squibb submitted that the reply, "No. One of the newer antidepressants is less likely to cause the sexual side effects that you may experience with TCAs and SSRIs" embraced several possible medicines that could be considered as newer than the TCAs and SSRIs such as moclobemide and mirtazapine as well as nefazodone (Dutonin). At no point in the booklet was Dutonin or any other product name mentioned.

Bristol-Myers Squibb did not consider the booklet contravened Clauses 20.1 or 20.2 of the Code as members of the public were not being encouraged to request a prescription for the company's product.

RULING

The Panel noted that the booklet gave patients general information on how depression, and its treatment, might affect their sex life. No specific medicine was mentioned, either by brand name or by generic name. The Panel considered that the booklet might encourage patients to discuss their sexual problems with their general practitioners and that this was not necessarily unacceptable. The patients would not know that Dutonin was promoted by Bristol-Myers Squibb as having a low rate of sexual side effects.

The Panel noted that the answer to the question at issue stated that one of the newer antidepressants was less likely to cause sexual side effects than might be experienced with TCAs and SSRIs. The Panel noted the company's submission that there were products other than Dutonin which were also "newer". The Panel also noted that mirtazapine, referred to by Bristol-Myers Squibb, did not seem to be generally available in the UK and that moclobemide (Manerix) was available in April 1994 as the data sheet appeared in the 1994/5 ABPI Data Sheet Compendium.

The Panel considered that the booklet might encourage patients to ask their doctor for a prescription but not for a specific product. Even if the patient asked for "one of the newer antidepressants" it was still up to the doctor to decide which product, if any, to prescribe.

The Panel decided that, on balance, the booklet was reasonable in relation to Clauses 20.1 and 20.2 of the Code. No breach of the Code was ruled.

Complaint received **17 February 1997**

Case completed **3 April 1997**

CASES AUTH/500/2/97 TO AUTH/511/2/97 *NO BREACH OF THE CODE*

GP v GLAXO WELLCOME, DU PONT, BAYER, ZENECA, BRISTOL-MYERS SQUIBB, KNOLL, WYETH, SMITHKLINE BEECHAM, RHÔNE-POULENC RORER, PFIZER, ASTRA and ASTA MEDICA

Sponsorship of meetings

A general practitioner complained about the sponsorship of a number of meetings by Glaxo Wellcome, Du Pont, Bayer, Zeneca, Bristol-Myers Squibb, Knoll, Wyeth, SmithKline Beecham, Rhône-Poulenc Rorer, Pfizer, Astra and Asta Medica. It was alleged that non medical people attended. The Panel noted that in some cases the companies had no record of supporting the meetings. In other cases companies had supported the scientific sessions of the meetings and/or paid to exhibit. The Panel considered that the arrangements were not unreasonable. No breach of the Code was ruled in each case.

COMPLAINT

A general practitioner complained about meetings sponsored by a number of pharmaceutical companies. The complainant alleged that the sponsorship was in breach of Clause 19 of the Code. The meetings had been attended by non medical people such as spouses, children and friends. The complainant referred to the annual reunion of the Bangladesh Medical Association (BDMA) UK held on 4/5/6 August, 1995, at Park Hall Hotel, Chorley. (The complainant first said that this meeting was held in 1996 but on further investigation the complainant confirmed that it was held in 1995). The complainant also referred to meetings held on 5/6/7 July, 1996, at the Alton Towers Hotel (a Dhaka Medical College (DMC) reunion) and on 26/27/28 July, 1996, at the Telford Moat House Hotel (a BDMA reunion meeting).

Case AUTH/500/2/97

Allen & Hanbury's was alleged to have sponsored the 4/5/6 August, 1995, meeting at the Park Hall Hotel in Chorley and Glaxo Wellcome UK Limited was alleged to have sponsored the 5/6/7 July, 1996, at the Alton Towers Hotel.

RESPONSE

August 1995 meeting Glaxo Wellcome said there was no record of its sponsorship of the meeting on 4/5/6 August, 1995, at the Park Hall Hotel. Since the merger of Glaxo with Wellcome took place just a few months before this meeting date it had contacted the field manager and local representatives who would have been responsible for any meeting supported by Wellcome in that area at the time. They had no record of supporting such a meeting.

July 1996 meeting Glaxo Wellcome acknowledged that it did provide modest support to part of the medical meeting which took place over the weekend at the Alton Towers Hotel. A consultant in genitourinary medicine wrote to Glaxo Wellcome requesting sponsorship for a talk and pharmaceutical exhibition stand at the Dhaka Medical College reunion. The local representatives subsequently discussed the proposal with the doctor. It was agreed that Glaxo Wellcome would hire a space for an exhibition stand during the registration period on Saturday morning and the medical programme on Sunday morning for £500. The representative left before

lunch on the Saturday. There was a medical symposium on the Sunday morning consisting of 4 lectures from 9:30am to 1:30pm during which the promotional stand in the exhibition area adjacent to the lecture theatre was manned by Glaxo Wellcome. About 80-100 doctors attended the medical programme. The doctor gave a lecture on sexually transmitted diseases which was sponsored by Glaxo Wellcome and a speaker fee of £50 was paid. The representative left before lunch on Sunday.

Glaxo Wellcome submitted that its involvement was purely in providing modest support to the medical meeting which took place within the context of a medical reunion weekend. There was no involvement in or sponsorship of any social activities which may have been undertaken by accompanying non medical persons during the weekend.

Glaxo Wellcome supplied a copy of letter from the doctor to the sales executive at Wellcome regarding the sponsorship. This letter stated that it was expecting over 200 doctors to attend and that hopefully the seminar would be PGE approved. The letter ended with a post script "We feel that your product Valtrex will have an immense impact on the audience, as most of them are GPs".

PANEL RULING

General principles The Panel accepted that fees for exhibition stands often subsidised the overall cost of a conference/meeting. It was a question of whether the pharmaceutical company had agreed to pay the exhibition fee on the basis that the money would be used directly to pay for accompanying people such as spouses etc. In the Panel's view it was acceptable for pharmaceutical companies to pay a fee for an exhibition stand at a meeting provided that the arrangements complied with Clause 19 of the Code. The meeting must have a clear educational content, any hospitality provided by a pharmaceutical company must be secondary to the nature of the meeting and must be appropriate and not out of proportion to the occasion. Hospitality must not be extended to spouses and others unless they qualify as delegates in their own right. Further, all materials would need to comply with the Code and the exhibition should not be open to members of the public if promotional material for prescription only medicines was to be displayed.

* * *

The Panel noted that there was no record of Glaxo Wellcome sponsoring a meeting on 4/5/6 August 1995 and therefore ruled no breach of Clause 19.1 of the Code.

The Panel noted that the supplementary information to Clause 19.1 permitted the payment of reasonable honoraria and reimbursement of out of pocket expenses, including travel, for speakers.

The Panel noted that Glaxo Wellcome's sponsorship for the July 1996 meeting was for a talk and an exhibition stand. The meeting had a medical programme attended by 80-100 doctors. In the Panel's view it was not unreasonable for Glaxo Wellcome to pay a £50 speaker fee and £500 for an exhibition stand at the meeting. No breach of Clause 19.1 was ruled.

Case AUTH/501/2/97

Du Pont Pharmaceuticals Limited was alleged to have sponsored the meeting on 4/5/6 August, 1995, at the Park Hall Hotel, Chorley.

RESPONSE

Du Pont submitted that the meeting involved a PGEA approved clinical presentation on the morning of 5 August, 1995. The medical representative erected an exhibition stand and presented products and literature for doctors attending the meeting both before and at coffee breaks during the presentation. At the end of the presentation the representative dismantled the stand and left. The meeting commenced at 10am and concluded at 12:30pm. The company's sponsorship was £200.

Du Pont provided a receipt from the Bangledesh Medical Association in the UK for £200 to meet expenses for the clinical meeting, PGEA approved, at Park Hall Hotel, Chorley.

PANEL RULING

The Panel considered that the general principles noted above applied in this case.

In the Panel's view it was not unreasonable for Du Pont to pay £200 for an exhibition stand at the meeting. No breach of Clause 19.1 was ruled.

Case AUTH/502/2/97

Bayer plc Pharmaceutical Division was alleged to have sponsored the meeting on 4/5/6 August, 1995, at the Park Hall Hotel, Chorley.

RESPONSE

Bayer said that the meeting was attended by two of its representatives who between them had sponsored the meeting to a total of £600. The invitation to sponsor was extended by a GP in Lancashire and the payment consisted partly of a £100 speaker fee payable to another doctor who spoke to the conference on Asian diabetes.

The remaining £500 was for sponsorship of the meeting room and food for the delegates for the Bangladesh Medical Association meeting. The company's understanding was that it was to cover the meeting room and catering costs for doctors only. In return for the sponsorship fee, the two medical representatives attended with an exhibition stand. A medical exhibition was held outside the main conference hall. Bayer was also told that although some of the delegates to the meeting would be bringing their wives and families to the venue they would in no way be associated with the proceedings of the meeting nor the sponsorship fee requested. This was borne out during the medical exhibition where the Bayer stand was visited during meal and refreshment breaks by doctors only. Bayer agreed to sponsor the meeting on the clear understanding that the sponsorship did not extend beyond members of the health professions or appropriate administrative staff.

PANEL RULING

The Panel considered that the general principles noted above applied in this case.

It was not unreasonable for Bayer to pay a £100 speaker fee and £500 sponsorship for an exhibition stand and towards payment of room hire and refreshment costs for healthcare professionals only. The company had been assured that the sponsorship was not associated in any way with the presence of wives and families at the venue. The Panel ruled no breach of the Clause 19.1 of the Code.

Case AUTH/503/2/97

Zeneca Pharma was alleged to have sponsored the meeting on 4/5/6 August, 1995, at the Park Hall Hotel, Chorley, and the meeting on 5/6/7 July, 1996, at the Alton Towers Hotel.

RESPONSE

August 1995 meeting Zeneca submitted that it had provided £1,500 financial sponsorship towards a scientific seminar and in addition had an exhibition stand. The exhibition stand was manned by one of the medical representatives and situated in a room separate from the scientific seminar. The promotional material on the stand was largely Zestril material. The sponsorship related only to the scientific element of the meeting. No sponsorship was given to any social event and no hospitality was provided at any time to non healthcare professionals.

July 1996 meeting Zeneca said it was approached by a doctor with a request for sponsorship for the scientific seminar being held at the 50th anniversary reunion. The scientific seminar was held on Sunday, 7 July, from 10am until 1pm. The seminar comprised five lectures on medical subjects (HRT, herpes infection, hypertension in diabetics, cardiac failure and peptic ulcer) and was PGEA approved. Zeneca donated £3000 in sponsorship towards the scientific seminar and two cardiovascular lectures and in addition covered the costs of printing the meeting programme.

In addition to the scientific seminar there was a pharmaceutical company exhibition held at the hotel during the Saturday and Sunday. At the exhibition a number of pharmaceutical companies, including Zeneca, had exhibition stands. The exhibition was held in a separate room to the seminar and only medically qualified delegates were admitted. The Zeneca stand had promotional material for Zestril, Zestoretic and Zoladex and was manned by two medical representatives (one on each day) over the weekend. The medical representatives did not provide any hospitality to the delegates or to any of the accompanying persons and nor did they participate in any social activity. One of the representatives did attend the dinner on the evening of 6 July. His attendance was by special invitation of the organisers with a request to speak at the formal dinner. Non healthcare professionals were present at the anniversary reunion but not at the scientific seminar and none was in receipt of Zeneca hospitality.

Zeneca provided a copy of the letter from the doctor which stated that the donation to the meeting was for the scientific seminar and pharmaceutical exhibition and was not spent for non medical persons.

PANEL RULING

The Panel considered that the general principles noted above applied in this case.

The sponsorship had been in relation to the scientific part of each meeting and the cost of exhibition stands at each meeting. The Panel decided that Zeneca's sponsorship was not unreasonable and therefore ruled no breach of Clause 19.1 of the Code. This ruling applied to both meetings.

Case AUTH/504/2/97

Bristol-Myers Squibb Pharmaceuticals Limited was alleged to have sponsored the meeting on 4/5/6 August, 1995, at the Park Hall Hotel, Chorley.

RESPONSE

Bristol-Myers Squibb submitted that from its records it understood that a sum of £1500 was paid to the organisers of the Bangladesh Medical Association AGM in 1995. The payment secured exhibition space at the meeting and an opportunity for a slot in the meeting's medical education programme when an independent physician, a consultant psychiatrist, spoke about Bristol-Myers Squibb's product nefazadone. The company's records indicated that promotional material on the stand covered nefazadone and fosinopril. The records indicated that 57 general practitioners, 20 consultants, 5 senior registrars and 20 nurses attended the meeting. Three representative attended the meeting. The stand was in a separate location to the rest of the meeting. No hospitality was provided by the company and no sponsorship was given for any non educational programme or other activities that might have been arranged.

PANEL RULING

The Panel considered that the general principles noted above applied in this case.

The Panel noted that Bristol-Myers Squibb sponsorship was for a talk and an exhibition stand. The meeting had a medical programme attended by 82 doctors and 20 nurses. In the Panel's view it was not unreasonable for Bristol-Myers Squibb to pay £1500 to sponsor the event. No breach of Clause 19.1 was ruled.

Case AUTH/505/2/97

Knoll Limited was alleged to have sponsored the meeting on 4/5/6 August, 1995, at the Park Hall Hotel, Chorley.

RESPONSE

Knoll said that it believed it had supported the meeting via one of its local representatives. At the time of the meeting Knoll was in the process of moving from Maidenhead to Nottingham as a result of the purchase of Boots Pharmaceuticals and the formation of a new merged business. The records that had been located related to a representative who was no longer employed by Knoll.

As far as Knoll was concerned the support would be given in good faith towards the running of a medical meeting. Requests for support that the company had seen from the Bangladesh Medical Association had been accompanied by details of a *bona fide* medical agenda, usually with postgraduate accreditation. Knoll had no reason to believe that the meeting in question was any different. Knoll believed that it had sponsored the meeting for £846. This however had to be deduced from the fact that the representative who submitted the claim was covering the area in which the meeting took place and the timing was about right. Since the move of the company to Nottingham, the representative had left the company as had the regional manager. The records only recorded claims against the products but did not identify the individual meetings and the backup documents were not transferred in the move.

Knoll said that it did not sponsor non medical spouses to attend medical meetings.

PANEL RULING

The Panel noted that the response from Knoll was general given that the company could not find the documentation due to changes of staff and the move from Maidenhead to Nottingham. The Panel noted that if the sponsorship had been for the sum of £846 this was not unreasonable given the information supplied about the meeting from the other companies.

The Panel decided that in this case that there was no evidence that there had been a breach of the Code and no breach of the Code was thus ruled.

Case AUTH/506/2/97

Lederle was alleged to have sponsored the meeting on 4/5/6 August 1995 at the Park Hall Hotel, Chorley, and the meeting on 5/6/7 July 1996 at the Alton Towers Hotel.

RESPONSE

Wyeth submitted that its records showed that Lederle did not support either the meeting held on 4/5/6 August, 1995, at Chorley or the meeting on 5/6/7 July, 1996, at the Alton Towers Hotel.

PANEL RULING

The Panel noted the submission from the company and ruled no breach of the Code. This ruling applied to both meetings.

Case AUTH/507/2/97

SmithKline Beecham Pharmaceuticals was alleged to have sponsored the meeting on 4/5/6 August, 1995, at the Park Hall Hotel, Chorley.

RESPONSE

SmithKline Beecham said that it had failed to find any documentation of any such event being sponsored by SmithKline Beecham. However due to a change of personnel over the period and a change in the computerised tracking systems, the company could not categorically state that there was no SmithKline Beecham person in attendance.

PANEL RULING

The Panel noted that SmithKline Beecham to the best of its knowledge was not involved with the meeting. The Panel therefore ruled no breach of the Code.

Case AUTH/508/2/97

Rhône-Poulenc Rorer Limited was alleged to have sponsored the meeting on 4/5/6 August, 1995, at the Park Hall Hotel, Chorley and May & Baker was alleged to have sponsored the meeting on 5/6/7 July, 1996, at the Alton Towers Hotel.

RESPONSE

August 1995 meeting The representative attended on the Friday evening and during the day on Saturday. The stand was set up in an alcove area with literature and materials relating to Celectol, Zimovane, and Oruvail. One other person attended on the Friday evening to assist with the stand. The representatives' role was to man the stand for a time when the doctors were attending lectures. The stand was then dismantled. About £200 was paid in connection with the event.

July 1996 meeting Two representatives attended and a stand was erected displaying material relating to Menorest, Ikorel and Zimovane. The guest speaker in the afternoon focused on HRT. The representative concerned paid for exhibition space only to promote products to the doctors attending. There was no payment for food or accommodation. About £400 was paid in connection with this meeting.

Rhône-Poulenc Rorer said that both meetings were organised by the Bangladesh Medical Association. At the time the company agreed to part sponsor the meetings it believed in good faith that the meetings were for a national medical association and that non medical staff would not be present.

PANEL RULING

The Panel considered that the general principles noted above also applied in this case.

The Panel considered that the sponsorship money of £200 and £400 for the exhibition stands at the two meetings was not unreasonable. No breach of Clause 19.1 was ruled. This ruling applied to both meetings.

Case AUTH/509/2/97

Pfizer Limited was alleged to have sponsored a meeting held on 26/27/28 July, 1996, at the Telford Moat House Hotel.

RESPONSE

Pfizer said that in April, 1996, the representative covering Telford received a request from a member of the

Bangladesh Medical Association to sponsor a meeting to be held in Telford inviting doctors from all over the country. Pfizer provided a copy of the programme which included a number of topics on disease areas related to Pfizer products. Sponsorship and advertising was agreed. The charges were £250 per stand for one day and £200 for an advertisement in the relevant publication.

The meeting took place over three days Friday, 26 July, to Sunday, 28 July. Pfizer was only represented on 27 July. This day was chosen to be the day Pfizer took a stand as it had been informed that this was the day of the scientific programme. A list of attendees at the Pfizer stand was enclosed. This totalled 103 people. The company was informed by the course organiser that a separate room would be available for the pharmaceutical company exhibition but on arriving at the hotel the representative found that a separate room was not available and space was allocated in an area not normally accessed by the public, a corridor leading to the meeting room. No other non medical functions took place in the conference portion of the hotel on 27 July.

Pfizer was represented by four sales staff who reported that no discussions took place with non medical personnel. As the meeting was of doctors countrywide, the attendees were not known to Pfizer's staff who had to ask where anyone coming to the stand practised medicine. In this way only medical personnel were given information about Pfizer products. The material on the stand consisted of promotional material for Pfizer products.

At the end of the afternoon the Pfizer representatives packed up and left the hotel with no further involvement in the meeting and at no time was a meal or other function involving non medically qualified partners or families of members of the Bangladesh Medical Association sponsored or attended. Although it was not known exactly how the sum paid by Pfizer for sponsorship was spent, in the company's opinion the sum was well within the bounds of an acceptable contribution towards the sponsorship of scientific funtion of this kind.

PANEL RULING

The Panel considered that the general principles noted above applied in this case.

The Panel noted that the letter to Pfizer from the Bangladesh Medical Association said that there would be about 120 - 150 doctors attending the event with 65% of the participants being GPs and the remainder hospital doctors. Details of the lectures were also provided and there were four lectures to be given on the Saturday and three on the Sunday.

The Panel noted that Pfizer had been told that a separate room would be available for the exhibition but on arrival there was not a separate room and space was made available in the corridor. Pfizer had ensured that everybody attending the stand was a healthcare professional.

The Panel considered that it was not unreasonable for Pfizer to pay £200 for an advertisement in the relevant publication nor was the charge of £250 for an exhibition stand unreasonable. No breach of Clause 19.1 was ruled.

Case AUTH/510/2/97

Astra Pharmaceuticals Limited was alleged to have sponsored the meeting on 26/27/28 July, 1996, at Telford Moat House Hotel.

RESPONSE

Astra submitted that it did pay the Bangladesh Medical Association £500 for the exhibition of a promotional stand at the medical meeting which the company understood was educational in nature. It also paid an honorarium of £250 plus travelling expenses to a doctor who was one of the speakers at the meeting. According to the company's records 66 doctors attended the stand and the materials used pertained to Losec.

PANEL RULING

The Panel considered that the general principles noted above also applied in this case.

In the Panel's view it was not unreasonable for Astra to pay a £250 speaker fee for an hour's lecture plus £500 for the exhibition stand at the meeting. No breach of Clause 19 was ruled.

Case AUTH/511/2/97

Asta Medica Limited was alleged to have sponsored the meeting on 26/27/28 July, 1996, at the Telford Moat House Hotel.

RESPONSE

Asta Medica submitted that the meeting was organised and held by the Bangladesh Medical Association under a programme of continuing medical education. It was, to date, the only meeting of the Association to which Asta Medica had acted as a main sponsor. There were 197 doctors present which included a mix of general practitioners and hospital specialists. Three Asta Medica staff were present, one of whom presented a one hour paper on rhinitis covering physiology, pathology, diagnosis, differential diagnosis and treatments. This was followed by a 15 minute question and answer session.

Asta Medica had a small exhibition stand in the area where formal sessions took place. While it was apparent that some of the doctors had been accompanyed by their families, the formal sessions and small exhibition area were reserved exclusively for the physicians. Asta Medica supported the organisation and costs of the formal sessions (invitations, room hire, equipment, printing etc) with a grant of £3000. No grant was given to support the participation of individual doctors or the accommodation costs of participants. Asta Medica said that it had not been able to obtain a list of participants or the original programme from the association and it had not kept a copy on the file.

PANEL RULING

The Panel considered that the general principles noted above also applied in this case.

The Panel noted that Asta Medica had been the main

sponsor of the meeting which had been attended by 197 doctors. In the Panel's view it was not unreasonable for Asta Medica to be the main sponsor at a cost of £3000. The money was given to support the medical educational programme and was used to pay for room hire, invitations, equipment etc. A member of Asta Medica's staff had also given a presentation on rhinitis. The Panel did not think that the sponsorship was unreasonable in the circumstances and no breach of Clause 19.1 was ruled.

Complaints received 24 February 1997

Cases completed 14 May 1997

CASE AUTH/512/2/97

GLAXO WELLCOME v GEIGY

Foradil detail aid

Glaxo Wellcome made two allegations about a detail aid for Foradil issued by Geigy.

The Panel considered that a suppressed zero on a graph comparing the efficacy of salbutamol and Foradil gave an exaggerated impression of the impact of Foradil. A breach of the Code was ruled.

A table comparing the costs of salmeterol and Foradil clearly stated that it was based solely on the use of the lower dose of each product. Statements above the table indicated that the lower dose of Foradil was sufficient for the majority of asthmatics but that some might require the higher dose. The Panel did not consider that the table misled as to the overall cost of Foradil therapy as alleged and ruled no breach.

Glaxo Wellcome UK Limited made two allegations about a detail aid for Foradil issued by Geigy Pharmaceuticals (ref: G1909 September '96).

1 Graph headed "Foradil offers protection from nocturnal symptoms of asthma"

COMPLAINT

Glaxo Wellcome said that the graph compared mean asthma symptom scores (evening/at night) between salbutamol 400 micrograms and Foradil 12 micrograms over eleven weeks. The graph had been adapted from one of the reference papers and quite clearly showed the vertical axis to start from 0.25 rather than from 0. This exaggerated the difference between the two products and therefore misled. By not taking the axis down to zero, Glaxo Wellcome alleged that the graph was in breach of Clause 7.6 of the Code.

RESPONSE

Geigy said that it was suggested by Glaxo Wellcome that the graphic representation of the data exaggerated the difference between the two products and their relative effects on the mean asthma symptom score. Geigy did not agree that this was the case since the response to both medications was plotted against the same scale to form an accurate representation of the data cited.

Geigy was, however, aware of the supplementary information to Clause 7.6 of the Code which stated that particular care should be taken with graphs and tables to ensure that they did not mislead. Whilst the graph in question contained a supressed zero axis, Geigy submitted that it was not a misleading comparison of the efficacy of Foradil compared with that of salbutamol as suggested. Geigy was concerned, however, that health professionals should obtain an accurate impression of the efficacy of both products and recognised that failure to take the axis to zero might, at a cursory glance, create a false impression of the impact of Foradil on the mean asthma symptom score. Geigy would therefore take appropriate steps to correct this scale in this graphical representation of the data down to zero.

PANEL RULING

The Panel considered that by failing to have a zero axis, the graph gave an exaggerated impression of the impact of Foradil on mean asthma symptom score and noted that Geigy accepted that that might be so and intended to correct it. A breach of Clause 7.6 of the Code was ruled.

2 Doses used in price comparison

COMPLAINT

Glaxo Wellcome said that the detail aid compared the cost of Foradil at 12 micrograms per day (86p) to salmeterol 50 micrograms per day at £1.07 for the disk inhaler and £1 for the Accuhaler. In a previous case (Case AUTH/394/2/96), the Panel had ruled that Geigy had misled and was in breach of Clause 7.2 of the Code for failing to inform doctors that between 20 and 35% of patients were on higher doses of Foradil. In the present case, Geigy had once again failed to remind doctors that 20 to 35% of patients might need the higher dose (24 micrograms bd) of Foradil which worked out at £48 for 28 days' treatment or £1.72 per day. Geigy acknowledged that this dose might be needed in smaller case text towards the bottom of the relevant page. Glaxo Wellcome alleged that the price comparison was misleading and in breach of Clause 7.2 of the Code.

RESPONSE

Geigy noted that Glaxo Wellcome had drawn attention to the outcome of Case AUTH/394/2/96 in which the claim of 20% reduction in cost compared with salmeterol was found in breach because it was not qualified by details as to the doses used for the basis of the claim. Geigy did not

agree that the table in question in the detail aid created the same impression.

The table was clearly headed by the statement "For patients controlled on the lower dose of each therapy Foradil costs less than the only other long-acting β_2-agonist given by dry powder inhaler". All of the cost comparison data presented served to qualify this table heading and related, for all three products, to the lower approved dose of therapy. It was difficult to imagine how the association between the table and the heading relating to the lower doses could be made clearer, other than perhaps enclosing it in some type of border. In addition, details of the recommended dosage for Foradil were clearly given at the top and bottom of the page.

Geigy had not been able to identify published studies which would enable it to establish the percentage of patients who required the higher doses of salmeterol compared to those requiring the higher doses of Foradil and nor had Glaxo Wellcome provided Geigy with the data as requested from it. There was, however, data to suggest that the average daily dose prescribed for salmeterol and Foradil was the same in everyday practice (approximately 2.1 doses per day) ie, the lower dose. This made the cost comparison for the lower dose of the two products highly appropriate for the prescriber. Geigy did not accept therefore that the table was grossly misleading and nor did it feel that it represented a contravention of its previous agreement with the Authority regarding cost comparisons for Foradil.

RULING

The Panel noted that in the previous case referred to by Glaxo Wellcome no details were given about the doses used as a basis for a claim that Foradil cost 20% less than salmeterol. It did not consider that the previous case was relevant to the complaint now before it.

The Panel considered that the page in the detail aid adequately explained the basis of the cost comparison. It stated that for the majority of patients a maintenance dose of Foradil of 12 micrograms bd would be sufficient to protect against asthma symptoms and that a minority of patients, those with severe asthma, might require the higher dose of 24 micrograms bd to achieve adequate control of symptoms. The cost comparison was in fact on the basis of 12 micrograms of Foradil twice a day and salmeterol 50 micrograms twice a day rather than 12 micrograms and 50 micrograms respectively per day, as stated by Glaxo Wellcome.

The page then went on to make it clear that the cost comparison was related to patients who were controlled on the lower dose of each therapy. Lower down it referred to the higher dose of Foradil needed in severe cases by the statement "severe cases - 24mcg b.d.".

The Panel did not consider that the table misled as alleged. It was clearly comparing the cost of 28 days' treatment and the cost per day of Foradil and salmeterol (in two types of inhaler) in respect of those patients controlled on the lower dose of each. No breach of the Code was ruled.

Complaint received **26 February 1997**

Case completed **15 April 1997**

CASE AUTH/513/2/97

SANDOZ v FUJISAWA

Letter on Prograf

Sandoz made a number of allegations about a letter on Prograf sent by Fujisawa. The letter referred to the impending discontinuation of the original formulation of cyclosporin (Sandimmun) and encouraged doctors to switch patients stablized on this product to Prograf as opposed to the new formulation of cyclosporin (Neoral).

The Panel considered that by not stating that it was the original formulation of cyclosporin which had been used in efficacy comparisons with Prograf, the letter was misleading in breach of the Code. In addition the dose of Sandimmun used in the cited studies was less than the licensed dose which was unfair and in breach of the Code.

A claim regarding transferring patients from Sandimmun to Prograf, was based on data comparing patients stablized on either Sandimmun or Prograf. The use of this data to imply that patients stablized on Sandimmun should be switched to Prograf as opposed to Neoral was ruled to be misleading. In addition the letter failed to state which formulation of cyclosporin had been used in the studies which was also ruled to be misleading in breach of the Code.

The Panel ruled no breach with regard to the use of cyclosporin tolerability data from paediatric heart transplant patients as the product was licensed to treat such patients even though Prograf was not.

The Panel ruled that the context in which cost effectiveness data had been used and the failure to state which formulation of cyclosporin was involved was misleading in breach of the Code.

The Panel ruled no breach with regard to the content of the Prograf prescribing information.

Sandoz Pharmaceuticals made a number of allegations about the promotion of Prograf by Fujisawa Limited. The material in question was a letter signed by the sales & marketing director. It was headed "Cyclosporin switching: Is Prograf the answer?". The letter referred to the impending discontinuation of the original formulation of cyclosporin (Sandoz's product Sandimmun) and stated that treatment options would be either a new microemulsion formulation of cyclosporin or Prograf (tacrolimus). The letter had been sent to renal and liver units throughout the UK.

1 Efficacy comparisons between cyclosporin and tacrolimus

COMPLAINT

In correspondence with Fujisawa, Sandoz complained about a claim in the letter referring to "The lower incidence of acute and chronic graft rejection for Prograf compared to cyclosporin in both liver and kidney transplant recipients....".

Sandoz noted, however, that all of the references cited to support this claim used doses of tacrolimus above the licensed recommended dose and doses of cyclosporin below the licensed recommended dose. In addition, all of these studies compared tacrolimus with Sandimmun, the old oral formulation of cyclosporin, rather than Neoral (cyclosporin), the revised oral formulation of cyclosporin. The claim was therefore extremely misleading and clearly in breach of Clause 7.2 of the Code. Sandoz also alleged a breach of Clause 3.2 of the Code , which stated that the promotion of a product must be in accordance with the terms of its marketing authorization.

In its letter to the Authority, Sandoz said that it could not accept the principle that unlicensed doses of a competitor product could be used exclusively in this context, particularly in relation to a comparative efficacy claim for Prograf. It was clear that none of the references used referred to licensed doses of cyclosporin.

RESPONSE

Fujisawa said that the care of patients post-transplant was a specialist field being carried out at a relatively small number of centres. The references cited were of clinical studies carried out in many of the leading transplantation centres in Europe and the United States. The cyclosporin dosage used was based on the usual immunosuppressive regimens used at the individual transplant centres. To have done otherwise would have been unethical. Fujisawa had contacted the original investigators to confirm this. The company had received one reply of confirmation. The protocols for the studies were submitted both to the Medicines Control Agency and the relevant hospital ethical committees who approved the protocols including the cyclosporin dosage schedules.

Fujisawa said that although it might not mirror the data sheet dosage, the cyclosporin dosage in these studies did reflect the use of this product in major transplant centres in the UK. Thus the studies cited formed an accurate, balanced and objective comparison of Sandimmun and Prograf as they were used in the UK.

Fujisawa said that as it was the dosage of Sandimmun which had been questioned, Clause 3.2, which stated that a product should be promoted in accordance with its product licence, had not been breached. Fujisawa noted that Sandoz did not claim that the promotion of Prograf was outside its product licence.

PANEL RULING

The Panel noted that the letter had been sent by Fujisawa because Sandimmun (cyclosporin) was to be discontinued. In the future clinicians would only have a choice of two immunosuppressants, Neoral (a microemulsion formulation of cyclosporin) or Prograf (tacrolimus). The letter set out the choice and then asked "Which patients should be considered for Prograf conversion?" The Panel considered that in such a circumstance comparisons of Prograf with Sandimmun might not always be relevant given that Sandimmun was

to be discontinued. The Panel noted that Neoral was a different formulation of cyclosporin compared to Sandimmun and that the two products had different pharmacokinetic profiles (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97). Given the situation, clinicians would need to know how Prograf compared to Neoral.

The Panel noted that the area of immunosuppression was complicated with regard to the doses of agents used. Clinicians using the medicines would be experts in their field. The Panel accepted Fujisawa's submission that the doses of cyclosporin used in the cited studies reflected the current use of the product in major transplant centres.

The Panel noted that all of the studies cited in support of the efficacy comparisons between cyclosporin and Prograf had used Sandimmun not Neoral. The letter only referred to "cyclosporin" at this point and was not specific as to which formulation was involved. The Panel considered that given the purpose of the letter some clinicians would assume that the data presented was a comparison between Prograf and Neoral ie the two products between which they would have to choose and not between Prograf and the product about to be discontinued.

The Panel considered that by not being specific as to which formulation of cyclosporin was involved the letter was misleading. The Panel accepted that this was a specialist field and clinicians might use doses of products outside the licensed recommendations. The Panel considered, however, that it was unfair to compare Prograf with Sandimmun at doses below the licensed dose. A breach of Clause 7.2 of the Code was ruled.

The Panel noted that Clause 3.2 of the Code stated that "The promotion of a medicine must be in accordance with the terms of its marketing authorization and must not be inconsistent with the particulars listed in its summary of product characteristics or data sheet". The Panel noted that as the letter in question was promoting Prograf not cyclosporin there could be no breach of Clause 3.2 of the Code with regard to the dose of cyclosporin.

The Panel noted that in correspondence with Sandoz, Fujisawa had said that only the initial dosage of Prograf in one study was higher than recommended in the summary of product characteristics. Dosage was, however, adjusted according to trough plasma levels which were within the company's dosage recommendations. Dosages (median dosage in some references) used in other studies were within current dosage recommendations. The Panel assumed that Sandoz had accepted this explanation as an allegation of a breach of Clause 3.2 with regard to Prograf did not appear in Sandoz's letter to the Authority.

2 Recommendations to convert stable transplant recipients from Sandimmun to Prograf

COMPLAINT

In correspondence with Fujisawa, Sandoz noted that the letter in question contained the following two claims: ".... suggests that Prograf-based immunosuppression may be appropriate for many of the patients switching from the original cyclosporin formulation" and "Conversion is likely to benefit many patients because those receiving Prograf have been shown to be at a reduced risk of acute graft rejection, to have more potential for steroid reduction and to be less likely to experience cosmetic side effects".

Sandoz said that the references quoted in the letter in question all related to comparisons between stable transplant recipients receiving either tacrolimus or cyclosporin post transplant. They did not relate to stable transplant recipients who had been transferred from Sandimmun to tacrolimus as compared to those who had been transferred from Sandimmun to Neoral. This was coupled to the fact that all of the references used doses of tacrolimus above the licensed recommended dose and doses of cyclosporin below the recommended dose (see point 1 above). These references could not, therefore, be used to support the claim that stable transplant recipients might benefit from transferring from Sandimmun to tacrolimus. Unless specific data could be provided to support the claim, the statement claiming possible benefit for stable transplant recipients transferring from Sandimmun to tacrolimus was thus grossly misleading and in breach of Clause 7.2 of the Code.

In its letter to the Authority, Sandoz said that no direct comparative data was available to compare patients converted from Sandimmun to Prograf with patients converted from Sandimmun to Neoral. The papers that were cited referred to stable transplant recipients and not to the rate of rejection and/or side effects following conversion. In the absence of such data Sandoz did not consider that it was possible to make any statements regarding comparative risk of rejection or side effects as had been done.

RESPONSE

Fujisawa said that much was made in the letters of complaint it had received from Sandoz of the potential dangers of switching transplant patients stable on one product to an alternative immunosuppressant therapy. It was therefore necessary to reiterate that Sandimmun was being discontinued. All transplant patients currently stable on Sandimmun, all of whom had a lifelong requirement for immunosuppressant therapy, would have to be switched to alternative therapies. Thus if there was a danger in transferring stable transplant patients from Sandimmun it was not one of Fujisawa's making.

It was true that no direct comparative data were given comparing patients converted from Sandimmun to Prograf and those switching from Sandimmun to Neoral, however Fujisawa contended that it made no comparative claims between these two treatment schedules. The letter stated quite clearly that Prograf was one option for the physician to consider when the discontinuation of Sandimmun forced them to switch. The letter was headed "Cyclosporin switching: Is Prograf the answer?" and contained the following sentences "Which patients should be considered for Prograf conversion?" and "Prograf based immunosuppression may be appropriate for many of the patients switching from the original cyclosporin formulation".

Fujisawa said that the letter was to inform transplant specialists of the option to switch patients currently receiving Sandimmun to Prograf and thus comparisons of these two products were clearly appropriate. Specifically the letter stated: "..... Prograf-based immunosuppression

may be appropriate for many of the patients switching from the original cyclosporin formulation".

Fujisawa said that Sandoz was concerned because the cited clinical studies involved stable transplant patients receiving either Sandimmun or Prograf rather than the transfer of patients from Sandimmun to Prograf. There was a great deal of published information concerning the transfer of patients on Sandimmun to Prograf because of graft rejection and/or cyclosporin toxicity. However, safety and efficacy comparisons of Sandimmun and Prograf using these data would clearly not be appropriate. Thus the most appropriate comparisons in this situation (ie the transfer of patients on chronic Sandimmun to chronic Prograf) were of liver or renal transplant patients on chronic Sandimmun or Prograf therapy such as those in the cited clinical studies.

Most published information concerning the conversion of patients from cyclosporin to Prograf dealt with the rescue of grafts during acute or chronic rejection. This conversion was well accepted and well documented. Reviews of this "rescue treatment" were provided. However, if "stable" referred to the clinical condition of the patient in terms of graft function, there were published data to support the transfer of "stable" cyclosporin-treated patients to Prograf.

A number of studies had examined the use of Prograf in transplant patients switched from cyclosporin because of unpleasant side effects such as hirsutism, gum hyperplasia and growth retardation whose graft function and general clinical condition were otherwise good. Guy (1994) reported the successful conversion to Prograf (in terms of relief of adverse effects and continued graft function) of patients who had developed side effects during cyclosporin treatment (neurotoxicity, hirsutism, increased blood pressure). Egawa (1994) presented 8 patients with hypertension and 3 patients with hirsutism converted from cyclosporin to Prograf. These patients all had resolution of these cyclosporin-induced adverse effects with continued good graft function. Winkler (1993) converted 12 liver transplant patients experiencing cyclosporin-related complications to Prograf treatment.

Fujisawa contended that the claims made were an accurate reflection of the published evidence and so there was no breach of Clause 7.2.

PANEL RULING

The Panel noted that the papers cited in support of the claims in question related to comparisons between patients stabilized on either Sandimmun or tacrolimus. The studies were not comparisons of patients stablized on Sandimmun and then switched to either Neoral or tacrolimus which was the situation that would be facing clinicians as Sandimmun was to be discontinued. In the Panel's view comparative data relating to patients stablized on either Sandimmun or tacrolimus was being used to imply a claim that patients stablized on Sandimmun should be switched to Prograf as opposed to Neoral. The Panel considered that the use of the data in this way was misleading.

The Panel acknowledged that the discontinuation of Sandimmun presented clinicians with an unusual situation, forcing them to transfer patients who responded to, and were tolerant of, the product on to either Prograf or Neoral. The Panel accepted that clinical data reflecting this precise situation did not exist and that comparing data from the chronic administration of the medicines might be appropriate. The Panel noted , however, that none of the cited references detailing the chronic use of cyclosporin related to Neoral, only Sandimmun. The letter only referred to cyclosporin at this point and was not specific as to which formulation was involved. The Panel considered that some clinicians would assume that the data presented related to Neoral ie one of the products between which they would have to choose, and not Sandimmun the product about to be discontinued. The Panel considered that by not being specific as to which formulation of cyclosporin was being discussed the letter was misleading.

A breach of Clause 7.2 was ruled.

3 The transfer of children from Sandimmun to tacrolimus

COMPLAINT

In correspondence with Fujisawa, Sandoz referred to a section of the letter which stated "Several units have reported problems converting children to the microemulsion formulation of cyclosporin". One of the problems reported was reduced glomerular filtration rate and two references were cited in the letter in support of this statement. The letter went on to state that, compared to cyclosporin, there might be a lower incidence of this side effect with tacrolimus. One of the references cited with regard to reduced glomerular filtration rate involved paediatric heart transplant patients (Gennery A *et al* 1996).

In its letter to the Authority Sandoz said it did not think it was appropriate to use data from a heart transplant study in children with Sandimmun to substantiate the use of Prograf when conversion from Sandimmun to tacrolimus in such patients would not be a licensed option. Sandoz alleged a breach of Clause 3.2 of the Code.

RESPONSE

Fujisawa said that it had become clear from its own discussions with transplant centres and from published correspondence, most notably in the Lancet, that problems had arisen in transferring some patients from Sandimmun to Neoral. This was one of the concerns which had prompted the letter in question.

The section referred to continued the theme of earlier sections which had summarised those situations where problems had arisen following conversion from Sandimmun to the new microemulsion formulation. The section referred to described such problems in children. The reference queried by Sandoz described a 10% deterioration in glomerular filtration rate in 9 of 21 paediatric patients transferred from Sandimmun to Neoral. These references related to Sandimmun and there was no claim actual or implied about the use of Prograf in heart transplant patients. Prograf was not mentioned at all in this paragraph. The following paragraph, which did relate to Prograf and its comparison with Sandimmun, used completely different references in kidney and liver transplant patients. Fujisawa thus contended that there was no breach of Clause 3.2.

PANEL RULING

The Panel noted that the reference by Gennery *et al* was used to support a claim regarding possible tolerability problems with cyclosporin. The paper was not used to support a comparison between Prograf and cyclosporin and nor to support a claim for Prograf. The Panel noted that, according to the Sandimmun data sheet (ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97) treatment of paediatric heart transplant patients was a licensed option. The Panel, therefore, considered that it was not unreasonable to refer to the paper when reviewing data on the overall tolerability of cyclosporin. No breach of the Code was ruled.

The Panel was, however, critical of the letter in question as it talked about transplants but did not clearly state that, whereas cyclosporin could be used as an immunosuppressant in heart transplant patients, Prograf could not. The Panel considered that it would have been helpful if the point had been addressed and requested that its views be passed on to the company.

4 Cost Effectiveness

COMPLAINT

In correspondence with Fujisawa, Sandoz referred to the claim: "..... reductions in time taken to reach stable and effective trough levels and a reduced incidence of acute rejection episodes will increase the overall cost-effectiveness of Prograf therapy". Sandoz alleged that this was a hanging comparison as it did not make it clear what the cost effectiveness increase was being compared to. A breach of Clause 7.2 of the Code was alleged.

Sandoz had said that no references were given to support the claim and it had asked Fujisawa to provide the data. Fujisawa had referred Sandoz to a paper by McKenna *et al* but Sandoz said that this paper compared the cost of using either tacrolimus or Sandimmun. It did not make any reference to improved cost effectiveness if patients were converted from one to the other. As the claim specifically implied a cost of benefit of conversion, Sandoz alleged a breach of Clause 7.2 of the Code.

RESPONSE

Fujisawa said that the letter concerned the conversion of patients from Sandimmun to Prograf. Cost benefit comparisons of Sandimmun and Prograf had been published. McKenna *et al* examined the large multicentre clinical study in liver transplant patients. They examined the relative costs of Prograf and Sandimmun using two year data from the large multicentre clinical study in liver transplant patients. They examined the effect on overall cost of rejection, adverse events and retransplantation as well as the treatment costs and concluded that there was a cost advantage in favour of Prograf.

PANEL RULING

The Panel noted that in correspondence with Sandoz, Fujisawa had said that the claim in question related to Prograf in comparison to Sandimmun. The entire letter, and more specifically the paragraph which contained the claim, compared Prograf and Sandimmun. Thus although the comparator was not explicitly stated, it was implied. The Panel assumed that Sandoz had accepted this explanation as in its letter to the Authority Sandoz did not allege that Fujisawa had used a hanging comparison.

The Panel noted that the section of the letter containing the claim in question was headed "The procedure for Prograf conversion". The data used to substantiate the cost effectiveness claim, however, was derived from patients stabilized on either Prograf or Sandimmun and not from patients being transferred from one product to the other. The Panel questioned the relevance of comparing the cost effectiveness of Prograf to Sandimmun given that the latter was about to be discontinued. No data regarding the cost effectiveness of Neoral was presented. The Panel noted that the letter only referred to cyclosporin at this point and did not specify which formulation was involved. The Panel considered that some clinicians would assume that the data presented related to the conversion of patients from Sandimmun to either Prograf or Neoral but this was not the case. The Panel considered that the context in which the data had been used, and the failure to specify which formulation of cyclosporin was involved, was misleading and ruled a breach of Clause 7.2 of the Code.

5 Prescribing Information

COMPLAINT

In correspondence with Fujisawa, Sandoz pointed out that numerous side effects that were listed in the tacrolimus data sheet which appeared in the 1996/7 ABPI Data Sheet Compendium had been omitted from the prescribing information provided with the letter (eg Stevens Johnson Syndrome, pancreatitis, cerebral infarct, cardiomegaly and heart arrest). Whilst Sandoz appreciated that a statement reading "Other adverse events have also been reported in isolated cases" had been included in the abbreviated prescribing information, given the seriousness of the adverse events that had been omitted and the fact that they were clearly listed on the data sheet, Sandoz considered that their omission from the prescribing information was clearly in breach of Clause 4.2 of the Code.

In its letter to the Authority, Sandoz said that it did not consider that the Code's requirements for a succinct statement of side effects permitted the picking and choosing of side effects for inclusion. Whilst Sandoz acknowledged that the omitted side effects occurred only in isolated or rare instances, it considered that the severity of these events warranted their inclusion, particularly since other rarely reported events were listed.

RESPONSE

Fujisawa submitted that the prescribing information accurately reflected the Prograf summary of product characteristics (SPC). All adverse events reported as frequent, occasional or rare (ie at rates of 1- > 10%) had been listed. Cardiomegaly was included under septal or ventricular hypertrophy. Those "isolated" adverse events which had been reported most frequently (albeit at rates <1%) were also listed. Only those events which had been

reported in isolated patients, which had not been noted in clinical studies or in the published literature, were not listed. However it was clearly stated that other adverse events had been reported in isolated cases. This careful consideration of what was clinically relevant certainly could not be described as the "picking and choosing of side effects". To list every single event which had ever been associated with Prograf was a function of the SPC not of the prescribing information.

Fujisawa pointed out that Prograf should only be prescribed by physicians experienced in immunosuppresive therapy and the management of transplant patients. Prograf therapy required careful monitoring in units equipped and staffed with adequate laboratory and supportive medical resources. It was important to emphasise that in this specialised area it was inconceivable that a doctor would prescribe Prograf on the basis of the prescribing information without reference to the SPC and other specialist information.

PANEL RULING

The Panel noted that Clause 4.2 of the Code required prescribing information to contain a succinct statement of the side-effects, precautions and contra-indications, giving, in abbreviated form, the substance of the relevant information contained in the data sheet or SPC. The clause did not require every side effect to be included and so it was clear that some details would have to be left out. The Panel accepted Fujisawa's submission and considered that the prescribing information given for Prograf was reasonable. No breach of the Code was ruled.

Complaint received 28 February 1997

Case completed 20 May 1997

CASE AUTH/516/3/97 *NO BREACH OF THE CODE*

GENERAL PRACTITIONER v SANDOZ

Disease area campaign to the public

A group of general practitioners complained that the Stepwise programme run by Sandoz encouraged the general public to consult their GPs about fungal toenail infections and ask for a prescription for a new treatment for the condition. The complainants considered that it was disingenuous to pretend that a GP faced with such a request would choose anything other than Sandoz's product Lamisil. The complainants pointed to the increase in NHS spending which would result from this.

Two similar complaints had previously been received about the Stepwise programme and in each case the Panel had ruled no breach of the Code. This complaint was allowed to proceed as new evidence had been provided and no appeal had been made in the previous cases.

The Panel noted that the Stepwise programme was directed at health issues of the feet and/or toenails. None of the material provided to the public as part of the programme referred to any specific medicine. The Panel considered that the material would increase the public's awareness of the area and might encourage some people to visit their doctor to discuss possible treatment of fungal toenail infections. This was not necessarily unacceptable. From the information provided patients were not being encouraged to ask their doctor specifically for Sandoz's product Lamisil. It was not the only product to meet the treatment criteria in the helpline. The borderline between health information and the promotion of a medicine was a narrow one in this context. The Panel considered the materials were reasonable. The press advertisement was not an advertisement to the general public for a prescription only medicine. No breach of the Code was ruled.

On appeal by the complainants the Appeal Board considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake. The Appeal Board noted that issues of NHS expenditure were not encompassed by the Code. The Stepwise materials were considered to be of a high standard and not designed to encourage patients to request a specific medicine. The Panel's rulings of no breach of the Code were upheld.

A group of general practitioners complained about an advertisement in The Independent, 6 March 1997. The advertisement was headed "There's no disguising problem toenails" and featured a picture of a big toe with the nail bearing a false nose, moustache and glasses. The text said that thick, brittle, discoloured toenails might be caused by fungal infection. A free leaflet and advice was offered and a freephone number was given. The advertisement referred to the Stepwise programme and said that it was sponsored by Sandoz. The freephone number accessed a pre-recorded helpline on fungal nail infections and athlete's foot. The helpline began "... I expect you have telephoned because you'd like to know how to do something about an ugly toenail ..." and went on to say "Your family doctor can now prescribe effective treatments. The treatments which you take by mouth will also cure athlete's foot at the same time as the infected nail".

COMPLAINT

The complainants said that despite the rulings on two previous occasions that there had been no breach of the Code with regard to the Stepwise programme (Cases AUTH/313/6/95 and AUTH/458/8/96), they were still unhappy with the advertisement. In order to make their case easier to understand it would be best to completely ignore any references to fungal skin infections of the feet and concentrate purely on fungal toenail infections. While the complainants accepted that in theory there were other possible new oral treatments for fungal toenail infections, in practice they could not see any other safe alternatives to Lamisil, the medicine produced by the company advertising in the newspaper. Griseofulvin was excluded because it was clearly not a new medicine within the terms expressed in the helpline message. All the other medicines, including Sporanox, had very serious potential

side effects which would not be justifiable for a non life-threatening condition such as fungal toenail infection. Indeed, the advice in the latest edition of the British National Formulary was that liver function tests should be performed if a treatment exceeded one month. It was clear that there was only one reasonably safe medicine to use in this condition and it was disingenuous to pretend that the GP faced with a request from the patient for a prescription for the new medicine to treat fungal toenail infections could choose anything other than Lamisil.

In addition the complainants considered that even if there was an alternative medication to Lamisil, the advertisement would be unethical since all that happened here was that Sandoz used its money partly to promote prescriptions of its own medications and inadvertently also to promote prescriptions for its rival. The fact that Sandoz might inadvertently promote a rival, did not weaken the ethical error of what the company was doing. The complainants accepted that this second argument could be extended into a situation where such actions could become ethical. This would be in a situation such as hypertension, where it would be ethical for a drug company to produce a pamphlet which suggested to patients to persist with taking their hypertensive medication. That sort of situation was different because there were truly many different alternative drugs available of which only one might be produced by the advertiser and the promotion to the public would be in keeping with health authorities', the Government's and doctors' views that hypertension and the maintenance of treatment was important. The complainants were not aware of any public health campaign by the Government to encourage people to treat fungal toenail infections.

The complainants said that the Stepwise helpline stated that there were over a million people with fungal toenail infections. The price of six months' treatment of Lamisil was £250 so that the market in question was of £250 million which would have to be found by the Health Service. If as a result of this advertisement the spending within the Health Service went from, say, nil at present to £250 million, then the fact that the £250 million was shared between Sandoz and company X did not alter the complainants' feelings that such advertising was wrong.

On a separate but related matter, the complainants also enquired as to the relationship of the Stepwise Company to Sandoz. Was it a wholly owned subsidiary, was it a charity, had it any other income, had it any other purpose other than advertising fungal infections of the feet and, in particular, fungal toenail infection treatment?

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The Authority noted that two similar complaints had been received (Case AUTH/313/6/95 and Case AUTH/458/8/96) in which the Panel had ruled no breach of the Code. Paragraph 5.1 of the Constitution and Procedure states that if a complaint concerns a matter closely similar to one which has been the subject of a previous adjudication it may be allowed to proceed at the discretion of the Director of the Authority if new evidence is produced by the complainant. Further, the Director should normally allow a complaint to proceed if it covers matters similar to those in a decision of the Panel which was not the subject of an appeal to the Appeal Board. As new evidence had been provided, and no appeal had been made in the previous cases, this new complaint was allowed to proceed.

RESPONSE

Sandoz Pharmaceuticals (UK) Limited submitted that the aim of the Stepwise programme was to provide helpful information to the public about foot and nail care generally, as well as alerting people who suffered from some of the common foot and nail problems that they could be fungal in nature and thus infectious. Copies of the Stepwise programme materials, which had been devised to encourage people to take more interest in their own healthcare, were provided. In addition copies of the original mailing letters sent out in 1995 informing all GPs, dermatologists, pharmacists and chiropodists about the Stepwise programme were provided. Sandoz pointed out that the materials contained therapeutic area information and advice only and no reference to any prescription medicine. Sandoz did not, therefore, accept that there had been any breach of Clause 20 of the Code.

Sandoz did not accept the complainants' assertion that Lamisil was the only therapeutic option considered by general practitioners treating fungal nail infection. Sandoz's own market research of the therapeutic area demonstrated that this was far from being the case in practice. If drug therapy was considered appropriate there were a number of products licensed for the treatment of fungal nail infection as well as Lamisil, ie Trosyl, Loceryl, Nizoral, Grisovin, Sporanox and the most recently launched, Sporanox Pulse. In the case of the last mentioned product, the data sheet referred to liver function tests only in patients receiving continuous treatment for over a month. It would appear therefore that this product, with its three weekly pulsed dosing recommendation, which was licensed specifically for the treatment of fungal nail infection, had been developed to overcome the issue raised by the complainants for the parent compound.

Sandoz noted that the complainants had also introduced some factual inaccuracies in relation to the dosage schedule for Lamisil which was 6 weeks to 3 months for most patients with fungal nail infection rather than the blanket 6 months that was referred to in the complaint. The resulting calculation had thus exaggerated the potential costs of the management of fungal nail infection to the National Health Service.

Sandoz submitted that the Stepwise programme was based on research indicating that there was a large, untreated reservoir of patients in the community who did not recognise that they had a fungal infection, or who had received ineffective therapy in the past. This lack of efficacy, which might equally be the result of poor compliance or re-infection, had led them to believe that their condition was untreatable. In the case of athlete's foot, which was thought to affect 10-15% of the population in the UK, the problem was often lack of adequate advice on duration of treatment and good foot hygiene in the population of patients, only a quarter of whom would have discussed their condition with their doctor. If untreated , athlete's foot and onychomycosis served as reservoirs of infection which could spread to other parts of the patient's body, their family and into the environment, especially amongst users of communal

bathing places. It had been postulated that without an effective public health campaign, this level of ignorance in the community would lead to an increased prevalence of dermatophyte infection.

Sandoz did not agree with the complainants' view that onychomycosis was a trivial condition unworthy of a public health campaign, nor their assertion that advising patients on the management of fungal infection should be viewed differently from a Code of Practice perspective to providing compliance advice for hypertension medications.

Sandoz said that the current Stepwise programme, of which the advertisement in The Independent was a part, utilised exactly the same materials as those which had been the subject of review by the Panel on two previous occasions. It might be of relevance to note at this point that an additional booklet was currently being developed which would extend the advice provided by the Stepwise programme to common foot problems such as bunions and would compliment the "Know Your Nails: Identifying Nail Problems" booklet which provided advice on a number of common nail problems. Both booklets provided advice to patients on how to identify and manage such conditions and provided useful tips on how to keep the nails and feet healthy.

Sandoz submitted that it had always made very clear its association with the Stepwise programme and had accepted that anything sponsored by the company or carried out on its behalf was its direct responsibility. The company questioned, therefore, the relevance of the relationship of Sandoz with any of the agencies working on its behalf to this issue which related specifically to Clause 20 of the Code.

Sandoz said it was aware that the provision of educational materials of this kind to patients had been the subject of considerable controversy. In view of this it had carried out a thorough review of the regulatory framework and Code of Practice precedents on provision of information to patients and developed some clear guidelines for compliance before fully developing the Stepwise programme. A copy of this review was provided.

Sandoz recognised a commitment to health education, of which the Stepwise programme formed a part. It had devised the programme with the above factors in mind and in careful compliance with the Code of Practice to encourage patients to take more interest and responsibility for their own healthcare. It was clear from some of the correspondence received from patients that the programme was working in raising patient awareness and that advice received from the Stepwise materials had led to successful management of long term embarrassing fungal infection using a variety of treatments. The Stepwise programme materials contained no reference to any prescription medicine and, as such, Sandoz considered that they complied with Clause 20 of the Code.

PANEL RULING

The Panel noted that the materials provided by Sandoz were similar to those at issue in Cases AUTH/313/6/95 and AUTH/458/8/96. The materials provided in Case AUTH/516/3/97 consisted of a booklet "Feet & Nails Stamping Out Problems" (Step 1), three letters to healthcare professionals, a leaflet "How to recognise problem toenails when you see them" (Step 3) and a booklet "Know Your Nails - Identifying Nail Problems" (Step 5). A booklet "Stamping Out Athlete's Foot" (Step 2) provided by Sandoz in response to Cases AUTH/313/6/95 and AUTH/458/8/96 was not supplied.

The Panel noted that the press advertisement was headed "There's no disguising problem toenails" and bore a picture of a big toe. It was clear from the advertisement that the Stepwise programme was sponsored by Sandoz. The Panel considered, from its name, and the accompanying picture of a big toe, that it was clear that the Stepwise programme was directed at health issues of the feet and/or toenails. The telephone helpline clearly referred to fungal infections of the toenail. While some of the materials provided sometimes mentioned fungal nail infections generally, the Panel did not consider that, within the context of the Stepwise programme, these referred to fungal infections of the fingernails. Fungal infections of the fingernails were not specifically referred to in any of the materials provided.

The Panel noted Sandoz's submission that most patients with fungal nail infections would require Lamisil treatment for six weeks to three months. The data sheet for Lamisil (ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97) stated that treatment for periods of less than three months could be anticipated in patients with fingernail infection, toenail infection, other than the big toe, and in patients of a younger age. In the treatment of toenail infections, 3 months was usually sufficient although some might require treatment for six months or longer. The Panel considered that while the complainants might have overestimated the cost to the NHS of infected toenails by referring to a blanket six month course of Lamisil, the six weeks - three months course of therapy referred to by Sandoz would not be sufficient for all patients.

The Panel noted that none of the materials provided referred to any specific treatments. The telephone helpline contained the statement "Your family doctor can now prescribe effective treatments. The treatments which you take by mouth will also cure athlete's foot at the same time as the infected nail". The Panel considered that, by implication, this statement ruled out long established therapies, topical therapies and those licensed only for fungal nail infections without the additional indication of athlete's foot. The Panel noted that similar statements appeared in the two booklets "Stamping Out Problems" and "Know Your Nails" and the leaflet "How to recognise problem toenails when you see them" all of which were directed to members of the public.

The Panel noted that one of the requirements of Clause 20.2 of the Code was that "Statements must not be made for the purpose of encouraging members of the public to ask their doctors for a specific medicine". The Panel noted that none of the materials provided in support of the Stepwise programme mentioned any specific medicines. The Panel considered that the materials would increase public awareness of the disease area and might encourage some people to discuss possible treatments with their general practitioner. This was not necessarily unacceptable. From the information provided patients were not being encouraged to ask their doctors

specifically for the Sandoz product, Lamisil. The Panel noted that while Lamisil did meet the treatment criteria referred to in the telephone helpline, it was not the only product to do so.

As it had observed when considering Case AUTH/458/8/96 the Panel was, however, concerned about the concept of a disease area campaign, sponsored by a commercially interested pharmaceutical company, being conducted in the national press. The public was being induced to seek medical advice and treatment. The borderline between health information and the promotion of a medicine was a narrow one in this context. The Panel nevertheless decided that the press advertisement was not an advertisement to the general public for a prescription only medicine and ruled no breach of Clause 20.1 of the Code. With regard to the telephone helpline and the booklets, the Panel considered that these were reasonable in relation to Clauses 20.1 and 20.2 and ruled that there was no breach of the Code.

APPEAL BY THE COMPLAINANTS

The complainants said that Sandoz had stated that the main aim of the Stepwise programme was to provide helpful information to the public about foot and nail care generally. The complainants' view was that the Stepwise programme existed to increase sales of Lamisil. In particular the complainants drew attention to Sandoz's document entitled "Direct to the consumer campaign for fungal nail infections" the first paragraph of which stated that "It provides the reasoning and explanation behind the Sandoz Pharmaceuticals (UK) Ltd campaign for increased public awareness of fungal nail infections to facilitate market development for Lamisil Tablets which are indicated for this condition". The complainants were surprised that the Panel did not remark on this. The fact that the booklet "Feet & Nails" (Step 1) devoted its first 5 pages to fungal toenail infections, the next 3 pages to athlete's foot (for which Lamisil was also indicated) and its last 2.5 pages to general foot health, the claimed purpose of the campaign, was then not surprising.

The complainants said that Sandoz had stated that there were a number of products licensed for use in fungal toenail infections. This was irrelevant, since only Sporanox and Lamisil fitted the criteria of medication which the patient was led to expect from their GP. The complainants did not accept Sandoz's claims that the existence of Sporanox Pulse meant that the Stepwise programme was acceptable because, as stated in their original complaint, they considered that it was wrong for Sandoz to advertise even if some of their financial benefit from sales was shared by Janssen who were not contributing to the advertising campaign. Secondly, it appeared to the complainants that Sporanox Pulse was a recent introduction, which they believed might have been introduced after the start of the Stepwise programme, which appeared to have started before January 1995 according to literature provided by Sandoz.

The complainants did not agree that they had exaggerated NHS costs. They had assumed one million sufferers, but an article in a supplement to the British Journal of Dermatology stated that the figure was nearly 20% higher. The complainants said they had ignored the costs of repeated courses of treatment, which would be inevitable for a minority of patients, the NHS costs of monitoring treatment and treatment of side-effects had also been ignored. However, the exact sum was not critical, and even taking the minimalist claims of Sandoz, this amounted to £60m which was an enormous sum.

The complainants said that they did not describe onychomycosis as a trivial condition in their complaint.

The complainants said that Sandoz had stated that the relationship of Stepwise to Sandoz was irrelevant, given that Sandoz had clearly stated that it sponsored Stepwise. The complainants contended that when one organisation sponsored another they would understand it to mean that those organisations existed separately, and for example, one was not just the marketing wing of the other. Therefore the complainants wished to know if Stepwise existed in any sense independently of Sandoz.

The complainants noted that neither the Panel nor Sandoz commented on their comments relating to one company advertising treatment, which would also benefit a rival, but cost the NHS.

The complainants noted that the Panel had considered that the telephone helpline and booklets were reasonable in relation to Clauses 20.1 and 20.2. The complainants did not agree since they believed that members of the public were being encouraged to ask their doctors to prescribe a specific medicine viz. a new oral antifungal for toenails. The complainants contended that this meant Lamisil, but even the proponents of Stepwise could only increase this to two possible choices at most.

The complainants said that they maintained the principle that NHS expenditure should be determined by balanced judgements about need, and not by drug companies or other providers of services.

RESPONSE BY SANDOZ

Sandoz did not deny that the management of fungal nail infection was an area of interest to the company since this was apparent to all prescribers who were familiar with the company's product portfolio. This was, however, also an area of considerable development over the last couple of years with an increasing number of products both topical and oral becoming available. Sandoz provided the following list of products licensed for the treatment of fungal nail infections: Canesten, Daktarin, Fulcin, Grisovin, Lamisil, Loceryl, Masnoderm, Phytex, Sporanox, Tinaderm Plus and Trosyl. Despite the arrival of these products, however, many patients remained surprisingly uninformed of the characteristics of fungal infection or that the fungal condition they had suffered for years could be effectively treated. The Stepwise programme was intended to rectify this situation and provide patients with sound advice with which to make an informed decision about their own care, ie whether to raise the issue of their fungal nail condition with their doctor or continue as they were. For those patients sufficiently concerned about their condition to phone the helpline and request the booklet, the Stepwise materials provided some useful advice on how to identify foot problems and their management. Once the patient had decided to discuss their condition with their doctor, the decision to treat and the choice of intervention remained with the prescriber. It was clear from Sandoz's own

research that the actions taken by general practitioners when faced with a fungal nail infection varied considerably.

Sandoz said that the complainants referred in their letter to the fact that the booklet "Feet & Nails" contained 5 pages on the management of fungal nail infections. It should be remembered that this booklet was sent out to those who had responded to an advertisement about such infections and therefore any additional information at this point could lead to confusion. A subsequent booklet entitled "Know Your Nails" (Step 5) expanded the area of nail care to include a variety of other conditions and their management.

Sandoz said that other materials produced for the Stepwise programme included the management of fungal skin infection, which the complainants requested be ignored in relation to their original complaint. There was also a leaflet "Stamping out Athlete's Foot" (Step 2) which was not sent with the response to this complaint as it did not form part of the direct response to the Stepwise advertisement but was provided for use in pharmacies where the choice of intervention was extensive. Since receiving the recent complaint Sandoz had also completed another Stepwise publication "Step Check" (Step 6) which again sought to broaden patients' awareness of common foot conditions and how they might be managed in line with the Stepwise programme's purpose of raising general awareness of foot health.

Sandoz said that the choice of intervention available to a prescriber was extensive. The Stepwise materials which were introduced in May 1995, advised patients that "their doctors can prescribe effective treatments and that those taken by mouth will also cure athlete's foot". There was no suggestion anywhere in the programme materials that the prescriber's choice was restricted to oral therapy and, as Sandoz had pointed out in its previous responses, both Trosyl and Loceryl lacquers were specifically indicated for this condition. To suggest that the prescriber's choice was in some way limited to two products was therefore incorrect. All products licensed for use in this indication had been subjected to careful review by the Medicines Control Agency, which had confirmed that the risk benefit ratio for their use was acceptable. With reference to the introduction of Sporanox, Sandoz confirmed that this product had been available for the treatment of fungal nail infection since early 1995.

Sandoz said that the complainants had referred to the potential cost of managing fungal nail infections in the community, based on the theory that all patients would receive Lamisil. Sandoz noted that during the years that the Stepwise programme had been in existence, there had not been the large increase in sales to which the complainants referred.

Sandoz said that it should also be noted that the advice provided by the Stepwise programme, to manage the feet correctly and to seek intervention in the management of athlete's foot, should prevent the condition progressing into the nails and to other members of the family and thus decrease the size of the pool of infected patients with fungal nail infection. This could, in fact, decrease the costs to the NHS of the management of this condition in the long term.

Sandoz accepted that the complainants did not refer to onychomycosis as a trivial condition but it was clear that a distinction was being drawn between the Stepwise programme and providing patients with information on compliance with antihypertensive therapy. Sandoz did not consider that there was an ethical difference involved in informing patients about any medical condition, where good compliance could lead to effective management and where a variety of interventions were available, as was the case with both hypertension and fungal nail infection. The Code did not distinguish between conditions of differing severity, therefore if it was permissible to have a public education campaign for a life-threatening illness, it was equally permissible for other disease states.

Sandoz reiterated that all materials used in the Stepwise programme were sponsored and therefore the responsibility of the company. However, it should be noted that the Stepwise programme was run on behalf of Sandoz by an external communications agency and its staff were not direct employees of the company. It was the activities of this company, carried out on Sandoz's behalf which were in question and provided all of these were within the Code, the relationship between the companies was irrelevant.

Sandoz noted that the complainants made reference to the cost of treatment of fungal nail infection to the NHS. As the company had pointed out, it could equally be argued that a health education campaign of this type was designed specifically to reduce NHS costs long term. If it was possible, by informing patients in this way, to remove some of the reservoirs of infection from the community, this could only benefit the patient, who was adequately treated and more able to avoid reinfection, and also the NHS which may only have to treat the patient once. Failure to inform the patient permitted the continued spread of a group of highly infectious organisms, through ignorance or worse the cost of treatment which was then wasted through poor aftercare, hygiene and re-infection. The benefit of health education campaigns in relation to infectious organisms was thus to decrease rather than increase the population of sufferers.

Sandoz contended that nowhere in any of the Stepwise materials was any reference made to any prescription only medication. Patients were not advised to ask for a specific product nor was there any suggestion that the prescriber's choice was in some way restricted only to oral medications. The exact wording, which was common to all materials, was "Your doctor can now prescribe effective treatments. The treatments which you take by mouth will also cure athlete's foot at the same time as the infected nail". Sandoz said that this definition did not exclude topical therapies but merely stated the obvious proviso that treating a nail infection topically would not deal with athlete's foot if the patient happened to be suffering from both at the same time.

Sandoz contended that the Stepwise programme materials did not breach Clause 20 of the Code. The company did not consider that, with the range of products available for the management of fungal conditions, the Stepwise programme encouraged patients to request a particular product or constrained prescribers to select particular products from the range of interventions available to them. It was clear that the choice of therapy and the decision to prescribe remained with the prescriber.

Sandoz stated that Stepwise had been running for 3 years and 130,000 people had responded. The Medicines Control Agency reviewed Stepwise in 1995 and no action was requested. The company's representatives stated that 23-27% of patients seeking advice for a fungal nail infection did not receive treatment. The clinical judgement was left to the physician. Lamisil received a licence for fungal nail infections in January 1992. Sporanox was licensed for fungal nail infections in April 1995 and Sporanox Pulse was licensed in April 1996.

FURTHER COMMENTS FROM THE COMPLAINANTS

The complainants said that whilst they accepted there were many medications that could be used for athlete's foot, the Stepwise programme helpline clearly stated that there was a new oral antifungal agent which patients were encouraged to ask their GPs for. "GPs can now prescribe effective treatments. The treatments which you take by mouth will also cure athlete's foot at the same time". This immediately ruled out the majority of medications since they were creams. Proprietary forms of griseofulvin did not count since these had been the stock remedy for many years. The complainants contended that the only possible interpretation for a GP would be that this was Lamisil, or perhaps Sporanox . In the case of Sporanox, this was not a practical alternative for GPs since liver function tests needed to be performed if treatment exceeded one month. The latter objection did not apply to Sporanox Pulse. However, the complainants believed that Sporanox Pulse was not available at the time the Stepwise programme started. It appeared in the September 1996 edition of the BNF but not in the March 1996 edition, whereas the Stepwise programme started in 1995. The complainants therefore reaffirmed their contention that, faced with a patient demanding a new oral antifungal agent for toenail infections from their GPs, for practical purposes at the start of the campaign and for months afterwards, Lamisil was the only alternative. The complainants accepted that when Sporanox Pulse was marketed there were two alternatives from which to choose.

The complainants said that in their opinion, if it was incorrect for a pharmaceutical company to advertise a prescription only medicine without naming the medicine when it had a monopoly of the market, then it did not cease to be wrong when one competitor appeared and they shared the market between two. The complainants also noted that Sandoz had not chosen to respond to comments they had made regarding the Sandoz document "Direct to the consumer campaign for fungal nail infections".

The complainants said that the essence of their complaint was that the helpline specifically requested patients to ask for a new oral antifungal treatment. The fact that there were other treatments was irrelevant. The advertisement put pressure on GPs to prescribe a new oral antifungal. The complainants noted that Sandoz had stated that Sporanox had been available since early 1995. However, in their previous letter the complainants had made specific reference to Sporanox Pulse, not Sporanox, and to the best of their knowledge this product arrived on the market after the Stepwise programme started.

The complainants considered that the fact that Lamisil sales had not increased considerably as a result of the Stepwise programme was irrelevant to their complaint. If the Code was broken but the breaking of it did not produce a great increase in sales, there remained no justification for breaking the Code.

The complainants hoped that Sandoz was correct in its view that attacking fungal infection in the community would save NHS costs. The complainants would, however, expect some evidence of this before accepting the argument. On the face of it the scale of potential costs to the drug bill would need to lead to extremely significant benefits in other areas of expenditure. The complainants suggested that the Appeal Board might explore which budget might benefit.

The complainants said that they understood that the Department of Health cooperated with pharmaceutical companies in certain promotional campaigns, in particular that for flu vaccines in the run-up period to winter. They could understand this as a matter of strong public interest where lives could be saved. However, the complainants said that if they accepted Sandoz's view that there was not an ethical difference involved in informing patients about any medical condition where good compliance could lead to effective management where a variety of interventions were available and that the Code did not distinguish between conditions of differing severity, then the pharmaceutical market would be totally unregulated and pharmaceutical companies would be able to advertise any prescription only medicines that they wished. The complainants did not consider that this was the purpose of the Authority.

With regard to the relationship between Sandoz and Stepwise, the complainants' contention was that the word "sponsor" implied that Stepwise was not totally funded by Sandoz. The complainants considered that the impression a member of the public would have was that this was an organisation interested in fungal toenail infection and to help its work Sandoz had contributed money. If, however, the Stepwise programme had no other funding at all apart from that from Sandoz, then the complainants considered that the public were being misled. The question of how much funding came from Sandoz to Stepwise and how much from other sources was relevant and should be made clear. Sandoz had failed to make clear the exact financial relationship of Stepwise to Sandoz. If Stepwise was entirely paid for by Sandoz, then to say it was merely sponsored was misleading.

With regard to Sandoz's response in relation to potential NHS cost savings of the campaign, the complainants welcomed these. Before they could accept any of these statements they would wish to have evidence to back them.

The complainants did not accept that the exact wording "Your doctor can now prescribe effective treatments. The treatments which you can take by mouth will also cure athlete's foot at the same time as the infected nail", implied that there were many different treatments and that some of them were oral. If this were the intention, then the phrasing should be such as: "Your doctor can now prescribe various effective treatments. Some of these treatments can be taken by mouth. The ones taken by mouth will also cure athlete's foot at the same time as the infected nail". This would make it perfectly clear that topical treatments might also be included as being

effective. The wording, as on the helpline, led members of the public to understand that the treatments were new and exclusively oral.

The complainants said that Sandoz had revealed the entire motivation behind the Stepwise programme in their document "Direct to the consumer campaign for fungal nail infection", which "provides the reasoning and explanation behind the Sandoz Pharmaceuticals (UK) Ltd campaign for increased public awareness of fungal nail infections to facilitate market development for Lamisil Tablets which are indicated for this condition". This was an admission that Stepwise was an advertising campaign to the public which was intended to promote Lamisil tablets. The complainants considered that this was a breach of the Code and if it were found not to be so, the complainants would question the appropriateness of a Code which did not criticise a campaign with such obvious acknowledged motives.

APPEAL BOARD RULING

The Appeal Board considered that patient education programmes were a legitimate activity for a pharmaceutical company to undertake provided that such programmes were in accordance with the Code. Such activities might facilitate the market development of the sponsoring companies' products but this was not necessarily in breach of the Code. Each case would need to be judged on its merits. The Appeal Board noted that Sandoz, in its document "Direct to the consumer campaign for fungal nail infection", had gone to some length to explore the regulatory and Code of Practice issues surrounding the Stepwise programme. The Appeal Board noted that the programme had been subject to a review by the Medicines Control Agency in 1995 but that no action had been requested.

The Appeal Board noted that the complainants had alleged that the Stepwise programme would escalate NHS prescribing costs. The Appeal Board noted that issues of NHS expenditure were not encompassed by the Code.

The Appeal Board considered that the Stepwise materials were of a high standard and would be useful in providing good quality patient education. The Appeal Board noted that the commercial success of the campaign was irrelevant, the important question to consider was whether or not the campaign met the requirements of Clauses 20.1 and 20.2 of the Code. In the Appeal Board's view, members of the public listening to the Stepwise helpline and reading the booklets might be encouraged to visit their doctor to discuss 'new' treatments particularly if therapy had failed in the past. Patients would also know from the materials that any oral therapy they received would cure athlete's foot at the same time as an infected nail.

The Appeal Board, while acknowledging that there was a fine distinction between education and promotion, did not consider that the information given via the Stepwise programme was such as to encourage patients to request a specific medicine. The Appeal Board considered that the telephone helpline and the booklets were reasonable in relation to the Code. The Appeal Board upheld the Panel's rulings of no breach of Clauses 20.1 and 20.2.

The appeal therefore failed.

Complaint received 12 March 1997

Case completed 28 May 1997

CASE AUTH/520/3/97

CLINICIAN v SERONO

Curosurf contract letter

A clinician complained that in a letter detailing the contract price for Curosurf, Serono was offering the product at a preferential price to selected neonatal units on condition that company representatives went to talk to staff to ensure they used the product correctly.

The Panel noted that the training of staff unfamiliar with a medicine was not necessarily unacceptable under the Code. In the Panel's view, however, Serono was making such training a condition of the preferential price of Curosurf. A breach of the Code was ruled because the Panel considered that the price of Curosurf was being used as an inducement to gain access to hospital staff.

A clinician complained about a contract letter for Curosurf issued by Serono Laboratories (UK) Limited which had been sent to him by a colleague. The letter, headed "All Wales Contract Pricing for Curosurf (Poractant Alfa)", had been sent to consultants and hospital pharmacists in Wales and set out the contract price for the product. It also gave some clinical details about Curosurf. The letter ended with an offer to units which had never used Curosurf that they could buy 20 vials of the product at a preferential price. The paragraph which detailed this offer ended with the sentence "It would be a condition of arrangement that we do come to talk to the unit staff, to help ensure that they get the best from Curosurf."

COMPLAINT

The complainant referred to the last paragraph of the letter and alleged that this was in breach of Clause 15.3 of the Code as an inducement was being offered to gain an interview.

RESPONSE

Serono rejected the allegation that a reduction in the price of Curosurf was offered as an inducement to gain an interview. It clearly stated in the letter that the "special arrangement" was for units that had not used Curosurf.

It was Serono's policy to offer training to all new users of Curosurf. Thus, the offer of the arrangement to come and talk to the unit was to ensure that they used a highly specialised, intensive care medication appropriately and were fully aware of the different administration technique and difference in speed of action from the surfactant they were currently using. Serono considered it part of its responsibility to ensure that health professionals had confidence in using its products, and thus an extensive education programme and ongoing staff training was available for all neonatal units.

Serono said that the letter in question and a copy of the Curosurf data sheet were sent in November 1996 to units who did not have experience of Curosurf, none of whom considered that Serono was "offering an inducement for an interview". Serono was shocked that the complainant had interpreted the letter as offering an inducement for an interview and, therefore, offered to write back to the units concerned clarifying its position.

RULING

The Panel noted that Clause 15.3 stated that "Representatives must not employ any inducement or subterfuge to gain an interview". The Panel considered that this clause was as applicable to companies as it was to individuals.

The Panel noted that the last sentence of the letter in question stated that "It would be a condition of arrangement that we do come to talk to the unit staff .... ". The Panel had some sympathy for Serono's position and recognised that training of intensive care staff previously unfamiliar with Curosurf would be an important issue in the correct use of the product and that the offer of such training was not necessarily unacceptable under the Code. In the Panel's view, however, in making such training a condition of the preferential contract price for Curosurf, Serono had gone too far. The reduced price for Curosurf was being used as a mechanism to gain access to hospital staff and a breach of Clause 15.3 was ruled.

During its consideration of this case the Panel noted that the letter in question was clearly promotional for Curosurf. There were a number of clinical claims for Curosurf. It was not a trade announcement exempt from the Code. The Panel considered that the letter should have included the prescribing information for Curosurf and requested that this be drawn to Serono's attention.

Complaint received **24 March 1997**

Case completed **12 May 1997**

CASE AUTH/521/3/97

DIRECTOR v CIBA

Alleged breach of undertaking

Glaxo Wellcome alleged that Ciba Pharmaceuticals was continuing to use a leavepiece which had previously been ruled to be in breach of the Code. The matter was taken up by the Director of the Authority as a complaint under the Code.

The Panel noted that although Ciba had made considerable efforts to withdraw the item in question it appeared that not all the copies of the leavepiece had been returned to head office. It had been let down by its representatives for whom it must take responsibility. Ciba had failed to comply with its undertaking and a breach of the Code was ruled. The company's failure to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry. The Panel therefore also ruled a breach of Clause 2 of the Code.

COMPLAINT

Glaxo Wellcome UK Limited complained that Ciba Pharmaceuticals was continuing to use a leavepiece for Foradil which had previously been ruled to be misleading in breach of Clause 7.2 of the Code (Cases AUTH/394/2/96 and AUTH/407/3/96).

Glaxo Wellcome said that one of its representatives in North London had recently been handed the leavepiece by a general practitioner. The company understood that similar activity had occurred in central Scotland.

In view of the fact that the complaint involved a possible breach of undertaking, the matter was taken up as a complaint by the Director of the Authority as the Authority itself was responsible for ensuring compliance with undertakings. This accorded with guidance previously given by the Appeal Board.

RESPONSE

Ciba said it was concerned to hear that copies of the leavepiece had been found to be still in circulation since immediate and extensive action was taken by the company to withdraw it from circulation following the previous Code of Practice rulings.

On 25 March, 1996, a letter was sent to all representatives with clear instructions to discontinue the use of the materials immediately and return all remaining stocks to head office for destruction. A copy of the letter was provided. In addition a follow up letter was sent on 1 April, 1996, requesting all representatives to sign a declaration that they had complied with the instructions to return all copies of the material relating to the Code of Practice complaints. A copy of the follow up letter was provided. Clear instructions were also communicated to all agencies responsible for the production and distribution of Foradil promotional materials that these particular items were no longer acceptable and should be destroyed.

Ciba was unable to offer an explanation for the incident

reported by Glaxo Wellcome but could only conclude that possibly, through some oversight, a residual number of leavepieces escaped the recall process and came into the possession of a new representative unfamiliar with the issues involved in the literature recall last year. It was not the company's intention to continue to use the item as part of the active promotion of Foradil.

To ensure that there could be no repetition, a repeat recall notice had been sent to all representatives together with clear instructions to review immediately all stocks of promotional materials held and under no circumstances to use the item in question to promote Foradil. A copy of the repeat recall notice was provided by the company. The company apologised for the incident.

RULING

The Panel noted that the company representatives and others had been instructed by letter to cease using the leavepiece and other promotional materials. The follow up letter, dated 1 April, 1996, had required representatives to sign to say that they had returned copies of various promotional materials, including the leavepiece in question. The company should have had procedures to ensure that materials provided to new representatives were current and not, as appeared to have happened in this case, materials that had been withdrawn.

The Panel noted that the company had taken action to comply with the undertaking but that apparently not all the copies of the leavepiece had been returned to head office for destruction. Ciba had failed therefore to comply with its undertaking. The Panel ruled a breach of Clause 21 of the Code.

The Panel considered whether there had also been a breach of Clause 2 of the Code in view of the fact that the use of the leavepiece represented a failure to comply with the undertaking and assurance previously given.The Panel noted that the company had made considerable efforts to withdraw the material. It had been let down by its representatives. Nevertheless the company had to take responsibility for the failure of representatives to withdraw the material regardless of what instructions had been issued. The Panel decided that the company's failure to comply with the undertaking brought discredit upon and reduced confidence in the pharmaceutical industry and therefore ruled a breach of Clause 2 of the Code.

The Panel noted that the Constitution and Procedure required it to report a company to the Appeal Board if it failed to comply with the procedures or if its conduct in relation to the Code warranted consideration by the Appeal Board (Paragraphs 8.1 and 8.2). The Panel decided that the circumstances did not warrant reporting Ciba to the Appeal Board.

Complaint received **27 March 1997**

Case completed **2 May 1997**

CASE AUTH/522/4/97

GP v SANDOZ

Supply of a promotional aid

A general practitioner complained about the supply of a promotional aid for Lamisil by Sandoz Pharmaceuticals. The complainant had replied to a mailing from Sandoz which offered to send a disposable camera. The complainant believed that as the mailing said "send" this implied by post. A representative had telephoned the complainant to ask for an appointment. It was mentioned that the representative needed to deliver the camera.

The Panel did not consider that the use of the word "send" was misleading even if a company intended to have the item delivered by a representative. No breach of the Code was ruled in this regard. The Panel considered that it was not unreasonable for the complainant to have gained the impression that he was obliged to see the representative in order to receive the camera. It had been used as an inducement to gain an interview. A breach of the Code was ruled.

A general practitioner, complained about the supply of a promotional aid for Lamisil issued by Sandoz Pharmaceuticals.

COMPLAINT

The complainant explained that he was sent some information which invited him to apply for a free disposable camera. The return card stated that Sandoz would send the item. A number of pharmaceutical companies offered items asking the recipient to specify a time for a representative to call. The complainant never requested such items as he did not see representatives. On this occasion, as the card specified that the camera would be sent, the complainant replied thinking he could give the camera to his children to experiment with. In due course a representative phoned and asked for an appointment. The complainant had not made a copy of the card and the representative told the complainant that he had requested the camera and that it required her to deliver it. Since the complainant had sent the card back and it bore his signature, he agreed to see the representative and the camera had been received.

The complainant said that what he objected to was that he specifically did not request a visit from the representative, but asked the company to send the camera. If the company was not prepared to send things, but insisted on a representative calling, then it was only fair that this was specified on the literature. Under the circumstances, the complainant regarded the appointment made with the representative as being obtained by devious means and alleged that the behaviour was in breach of the Code.

RESPONSE

Sandoz was concerned to hear about the complaint. The

mailing to which the general practitioner referred was sent out as part of a targeted mailing campaign in November / December 1996 (LAM96/22Oct96). The mailing offered the GP the opportunity of obtaining a complimentary disposable camera by returning a reply paid card to the company. The camera was offered as a means for the general practitioner to record the outcome of treatment with Lamisil tablets, particularly in relation to dermatophyte skin infections.

Sandoz said that the reply paid card which formed part of the mailing did indeed state that a complimentary disposable camera would be sent to general practitioners who signed and returned the card. In this context the company accepted that there had been some misunderstanding between the company and the recipient. From the company's perspective sending items of this type did not necessarily mean using the postal service, but rather the most effective delivery system available which, in this case, because of the nature of the item, was considered to be via the field based representatives.

The company was concerned that the complainant considered that the granting of an interview had been in some way conditional on delivery of the camera since this was certainly not the company's intention or purpose in providing this service. Sandoz pointed out that over 2,000 cameras were delivered in the same way, with no similar problems. Routine training for all representatives included clear guidance on their responsibility under the Code. It was made very clear that no inducement or subterfuge might be used to obtain an interview. This message was repeated in the representative's field operations manual which directed activity in the field.

In the light of the complaint, the company had investigated with the representative her interpretation of the events. On receiving the response from the general practitioner in question, the representative contacted the practice to identify a suitable time to deliver the camera and, if possible, to arrange an interview. At the time the doctor in question was not available but to the surprise of the representative he phoned her himself subsequently and arranged a suitable time for a meeting. There was no discussion on the telephone of the visit being a condition of receiving the camera and the subsequent meeting, as far as the representative was concerned, passed without issue. The complainant allowed her to complete her presentation of three of the company's products. The representative was therefore understandably concerned that her actions had been interpreted in that way and expressed herself surprised that the complainant had not either refused to see her, in which case she would have called and left the camera with the receptionist, or stated his concerns directly to her when arranging to see her or subsequently during the interview.

The company submitted that in light of the investigations there was no deliberate attempt by the representative to use devious means to gain an interview. The company did accept that there had been a misunderstanding of the arrangements whereby a complimentary item of this type was to be delivered to its recipient and would make every effort to avoid this in future mailing offers.

FURTHER COMMENTS FROM THE COMPLAINANT

The response from the company was sent to the complainant for further comment.

The complainant said that his complaint was about the mailing sent by the company which offered to send a camera and not about the representative. Sandoz thought that there was a misunderstanding about what the card said and Sandoz did not accept that the word "sending" meant that the postal service would be used but might mean a representative. The complainant enclosed photocopies of materials from other pharmaceutical companies, one of which specifically stated that items would be delivered by the representative and asked for a suitable time and date, and a second told the complainant that he could arrange to receive a number of items. In both instances the complainant would not reply on the grounds that he did not wish to see a representative. Since one specified that a representative appointment would be made, and the other used the word "receive", which could imply that the representative would deliver the items, it seemed reasonable for the complainant to decline these offers. In the case of Sandoz, the card specifically said "send" and the complainant believed that this implied by post. Had it stated on the card that a representative would call, the complainant would not have replied.

The complainant said that a representative phoned the surgery in March, asking the complainant to telephone her, leaving a number and asking for an appointment. The complainant provided a photocopy of the message book for that day which recorded the call.

The complainant said that he might have declined to phone the representative but considered this ill-mannered if he had inadvertently requested an interview and, in addition, the complainant had met on a previous occasion a representative with the same surname to receive some papers, although the person was employed by a different company. The complainant could not recall whether this might have been that representative and considered for reasons of courtesy that he should return the call. The complainant was amazed that the representative was surprised that he returned the call, since this would appear to be common courtesy. As it involved the making of an appointment, it would only be possible for the complainant to do this personally since he did not have a routine time available to see representatives and no member of staff could be expected to make the appointment. There was no discussion on the telephone that it would be a condition of receiving the camera but, on the other hand, it was stated that she had the camera and needed to deliver it. At the subsequent meeting the complainant made no comment to the representative since the complainant did not consider that she had been at any fault whatsoever. The entire fault lay with the company deliberately using misleading mailings by using "send" when it meant that a representative would deliver. The complainant did not raise the issue with the representative because he considered, again out of courtesy, that the appointment was made and she was doing her job to the best of her ability. The complainant was therefore prepared to give her the time and courtesy that he would expect of any other professional person doing their job.

The complainant accepted that no deliberate attempt was made by the representative to use devious means. However, devious means had been used by the deliberate wording of the company to imply that a postal delivery would be made and then a telephone call from the representative to arrange delivery of the item which implied that a contract had been made between the complainant who returned the card and the company to have the item delivered. Although it might not be stated, the complainant believed there was an implication that, having accepted something would be delivered by the representative, there was an implied expectation that the representative would be able to talk to the doctor concerning whatever product they might be trying to promote. Although these implications might not actually be true, the complainant did not think it was entirely clear in the mailing or in the general information given to doctors that they could refuse to see a representative in the event of any misunderstanding of this sort. If Sandoz's defence of its action was upheld, then it was time the Code was less vague so it could be quite clearly understood by companies what was meant by "send" and also that all doctors should receive a copy of the guidelines so that they knew what the company understood by the agreement.

The complainant reiterated that the fault lay entirely with the company and the wording of the mailing. He had no personal complaint about the representative who was professional, courteous and obviously only doing her job to best of her ability and it was because of this reason that the matter had been taken up with the Authority rather than complaining to the representative at the time of the visit since the complainant did not consider that it was her personal responsibility and nor would she have the authority to go back to the company and make any suitable representation.

PANEL RULING

The Panel noted that the mailing referred to Lamisil and included a reply paid card for the recipient to sign beneath the statement "Please send me a free disposable camera". The Panel noted that a number of companies stated on their mailings that a representative would call. In the Panel's view, even if a mailing stated that a representative would call to deliver a requested item but the doctor was not available to see the representative, the item had to be left for the doctor, otherwise it became an inducement to gain an interview in breach of Clause 15.3 of the Code. The Panel accepted that items offered on mailings were often delivered by representatives.

The Panel did not consider that the use of the word "send" was misleading even if a company intended to have the item delivered by its representative. No breach of the Code was ruled in this regard. It was up to the representative to ensure that the method of delivery could not be seen as an inducement to gain an interview with the recipient.

The Panel noted that Sandoz said that the representative had telephoned the surgery to arrange a suitable time to deliver the camera and, if possible, to arrange an interview. The record of the call supplied by the complainant gave the representative's name and stated "Re camera, would like to arrange an appt to see you". The Panel considered that the representative had given the impression that some contact with the intended recipient was necessary in order for the camera to be delivered.

In the Panel's view, it was not unreasonable in the circumstances for the complainant to have gained the impression that he was obliged to see the representative in order to receive the camera. This meant that it had been used as an inducement to gain an interview. The Panel therefore ruled a breach of Clause 15.3 of the Code.

The question of the suitability of a disposable camera as a promotional aid had been taken up with Sandoz under the provisions of Paragraph 16 of the Constitution and Procedure (Case AUTH/542/5/97).

Complaint received **1 April 1997**

Case completed **11 June 1997**

CASE AUTH/523/4/97

DERMAL LABORATORIES v PANPHARMA

Promotion of Movelat

Dermal Laboratories made a number of allegations about a price comparison chart and leaflet for Movelat issued by Panpharma.

The Panel ruled a breach of the Code as other companies' brand names had been used on the price comparison chart without obtaining the prior consent of the proprietors. The Panel ruled that the chart, which claimed specific cost savings with Movelat compared to other topical NSAIDs, was misleading in breach of the Code as it took no account of variable usage rates.

A claim in the leaflet that Movelat was cost effective related to a simple comparison of the prices of various topical NSAIDs. The Panel considered that "cost effective" should take into account other factors such as relative efficacy and side effects etc and so ruled that the claim was misleading in breach of the Code. The Panel did not, however, consider that the claim "1st line treatment" incorporated the use of a superlative and so no breach of the Code was ruled.

Dermal Laboratories Limited complained about the promotion of Movelat by Panpharma Limited. Dermal said that the materials at issue, a price comparison chart (ref X13.3) and a leaflet (ref MM3F), had recently been mailed to general practitioners. Panpharma was not a member of the ABPI but had nevertheless agreed to comply with the Code.

The allegations were considered as follows:

1 Use of other companies' brand names

COMPLAINT

Dermal alleged that the price comparison chart was in breach of Clause 7.10 of the Code as it named a variety of other branded products. Dermal could not speak for the other companies whose products were mentioned on the chart but said that no consent had been sought from Dermal for the use of the brand name Ibugel.

RESPONSE

Panpharma accepted that the price comparison chart was in breach of Clause 7.10 of the Code by using other companies' brand names without the consent of the relevant company. It said that the chart was intended for representative use only. Panpharma had recalled all the outstanding charts from the sales force and other materials which had similar charts.

RULING

The Panel ruled a breach of Clause 7.10 of the Code as the price comparison chart had referred to other companies' products by brand name and prior consent had not been obtained.

2 Comparison of costs

COMPLAINT

Dermal alleged that the price comparison chart was in breach of Clause 7.2 of the Code. The supplementary information to Clause 7 of the Code in relation to price comparisons required evidence to be shown that products were comparable and that usage rates were similar. No evidence had been provided, and nor did it exist, to demonstrate any such similarities between Movelat and Ibugel.

RESPONSE

Panpharma said that it was well accepted that differences in efficacy of non steroidal anti-inflammatory drugs (NSAIDs) had not been proven. This statement had been reiterated in numerous publications, including the MeReC bulletin. Copies were provided. In accepting the fact that the efficacy of all the products was similar, the distinguishing factor between them was the cost of each product in relation to unit dose, in other words the cost per gram.

RULING

The Panel noted that the supplementary information to Clause 7.2 of the Code stated that to compare the cost per ml for topical preparations was likely to mislead unless it could be shown that their usage rates were similar or, where this was not possible, for the comparison to be qualified in such a way as to indicate that the usage rates might vary. The Panel examined the price comparison and noted that it referred to common arthritic conditions. It was headed "TOPICAL NSAIDs Cost Saving Potential", one half of the chart gave for each product its name, the size of the tube and its cost. A further column was headed "Cost saving with MOVELAT". The differences between the prices of the named products and Movelat were given in this column.

The Panel considered that it would have been acceptable for Panpharma to simply have shown the size of the tube and the price of all the products listed in the chart. The use of the terms "cost saving potential" and "Cost saving with MOVELAT" implied that using Movelat gave a saving. In the Panel's view it was not as straightforward as simply the difference between the price of the named products and Movelat. The cost savings had to be related to dosage and frequency of use. For example, the dosage of Movelat was up to four applications daily of two to six inches, whereas Ibugel was to be applied up to three times daily with instructions that the product was to be applied thinly (ref ABPI Compendium of Data Sheets and Summaries of Product Characteristics 1996-97). There was no statement on the chart to point out that usage rates might vary. In the Panel's view, any calculation of cost savings should take account of the dosage regimens. The Panel considered that the cost comparison was misleading and therefore ruled a breach of Clause 7.2 of the Code.

3 Claim "Movelat. Cost-effective 1st line treatment"

COMPLAINT

Dermal alleged that a claim in the leaflet "Movelat. Cost-effective 1st line treatment" breached the Code in two respects. The claim "cost-effective" was a much abused term and no proper economic evaluation had been provided by Panpharma as required by Clause 7.2 of the Code. The claim "1st line" was a superlative which was inconsistent with the requirements of Clause 7.8 of the Code.

RESPONSE

Panpharma submitted that in the context of a price comparison for a range of products with no difference in efficacy, the least expensive would also be the most cost-effective. The advertisement was aimed at alerting general practitioners to budgetary issues with regard to the use of topical NSAIDs. The claim "Cost effective" was therefore justified in this context.

Panpharma submitted that it was generally accepted that for the relief of common arthritic conditions, topical treatments were considered as first line. Movelat was a topical NSAID and therefore fell into that category. The company had not claimed that Movelat was the first line treatment. It did not accept that first line was a superlative in the context presented in the leaflet. This was clearly demonstrated by the table beneath the claim which compared the price of other topical NSAIDs at £7 per 100g with the cost of Movelat therefore putting the whole claim into context.

RULING

The Panel noted that the supplementary information to Clause 7.2 of the Code stated that care must be taken that any claim involving the economic evaluation of a medicine was borne out by the data and did not exaggerate its significance. The Panel considered that no product could be cost-effective in isolation as there was always an element of comparison involved, even if no other product was mentioned. The claim for cost-effectiveness had been related to the cost of treatment in general. The leaflet had not dealt with the economic evaluation of the effectiveness of Movelat and no data had been provided to substantiate the claim. The Panel noted that Panpharma stated that all the topical NSAIDs were equally effective and the only difference was cost. In the Panel's view term "cost-effective" implied more than just a simple comparison of the cost of products. Other factors such as relative efficacy, incidence of side effects, etc, had to be taken into account. The Panel decided that the claim "Cost-effective" was misleading and ruled a breach of Clause 7.2 of the Code.

The Panel did not accept that the claim "1st line treatment" incorporated the use of a superlative. The Panel accepted the submission from Panpharma that for the relief of common arthritic conditions, topical treatments, were considered as first line therapy. The claim was not saying use Movelat first. The Panel ruled no breach of Clause 7.8 of the Code.

Complaint received **7 April 1997**

Case completed **8 May 1997**

CASE AUTH/524/4/97 *NO BREACH OF THE CODE*

DRUG & THERAPEUTICS COMMITTEE v ORGANON

Purchase agreement for Puregon

The Secretary of a NHS trust drug and therapeutics committee complained about a purchase agreement for Organon's fertility treatment, Puregon. The Panel noted that there was a shortage of urinary gonadotrophins (Humegon, Normegon and Pregnyl) and in the circumstances it was not unreasonable for Organon to limit supply of urinary gonadotrophins only to those customers who purchased other related Organon products. Given the difficult circumstances the Panel acknowledged that the solution to the problem, while not perfect, was a reasonable approach and on balance ruled no breach of the Code.

This complaint concerned a purchase agreement for Organon's range of gonadotrophins. Organon supplied a range of urinary products (Humegon, Normegon and Pregnyl) and one recombinant product (Puregon). The volume of urinary products a purchaser could order was dependent on how much of the recombinant product they needed. Urinary products could not be purchased without a concomitant order for recombinant products.

COMPLAINT

The secretary to a hospital NHS trust's drug and therapeutics committee, complained about the way Organon had forced the Trust to add Puregon to its formulary and its fertility clinic to prescribe it. The committee had been told that unless the Trust used Puregon, then the manufacturers would not allow it access to Humegon, Normegon or Pregnyl. A copy of the letter which contained the agreement from Organon stating the terms and conditions signed by Organon's customer services manager was provided. The complainant said that the trust might purchase either one Humegon or one Normegon for every three Puregon purchased and one Pregnyl for each ten Puregon purchased. The trust was under contract to provide a fertility service to the health authority, and this would not be possible without the full range of fertility agents. Therefore the trust considered that it had been left with no option but to comply with the terms offered.

Additionally, the complainant said that the company representative had been putting unnecessary pressure on the pharmacy purchasing manager to sign the agreement, which she had found intimidating.

The complainant considered that such linked deals were not only unethical and costly but nothing short of blackmail.

RESPONSE

Organon's response was as follows:

1 History of supply of urinary gonadotrophins

Organon said that a number of urinary gonadotrophins were available in the UK from Organon and Serono. The urinary gonadotrophins, which included menotrophin and urofollitrophin, contained follicle stimulating hormone (FSH) and luteinising hormone (LH) in various proportions.

The urinary gonadotrophins were derived, by purification, from the urine of post-menopausal women. Suitable women were carefully selected and screened as coming from areas, and having lifestyles, where the risk of viral contamination was minimised. These products had become subject to a relentless increase in demand as their use in the treatment of infertility had become more widespread, both nationally and internationally.

This increase in worldwide demand resulted, during 1995 and 1996, in supplies of these products being rationed on a worldwide basis. In the UK this rationing took the form of products being supplied almost on a "named-patient" basis. Clinics were advised by Organon (via the medical and pharmaceutical press and company representatives), not to undertake IVF cycles for patients unless a supply was available, for the patient, which would ensure a complete treatment cycle.

Such supply problems were not to the advantage of patients, clinicians or Organon. Customers who had arranged long-term supply contracts were protected, to a greater or lesser extent, from these problems.

Pharmaceutical companies had anticipated the increasing demand for infertility treatment and soon came to realise that the traditional source of the products would not meet the expected demand. They had therefore developed new products using recombinant technology which would substitute for, or even improve upon, urinary products.

2 Recombinant FSH products

2.1 Availability The introduction of recombinant FSH had helped to alleviate this problem in some countries. Both leading companies in the market introduced recombinant FSH products during 1996 and these products were now approved throughout Europe as well as a number of other countries. They were not, so far, approved in major markets such as the US, Canada and Japan, and so there still remained a shortage of supply of urinary gonadotrophins internationally.

2.2 Clinical profile The recombinant products, containing pure FSH but no LH activity, were suitable for use in the majority of patients undergoing infertility treatment. However a small number of patients (around 1%) required concomitant administration of very small quantities of LH. An appropriate product containing LH alone, in required quantities, was not available and therefore those products containing both LH and FSH were still required to treat such patients.

For that reason Organon had estimated the potential usage of the older urinary products both in the UK, and in other countries where recombinant products were available. As a result the company had "ring-fenced" supplies of urinary products for those patients in need of them, while supplying recombinant product such as Puregon for use in the majority of patients who did not require LH.

3 Supply in the UK Organon said that international demand for urinary products had led the company to implement a policy that in countries where it was possible to use recombinant products then these should be preferred over the supply of urinary products. In the UK Organon had been obliged to restrict the availability of urinary products to only those patients for whom there was a clinical need (for LH), approximately 1% of patients. Organon submitted that this action was further justified when Serono withdrew Pergonal, leaving Organon as the only supplier of an LH containing gonadotrophin.

4 Pregnyl Organon explained that Pregnyl was a preparation containing human choronic gonadotrophin (hCG). Serono had a similar product, Profasi. hCG was obtained from the urine of pregnant women and might be subject to similar restrictions of availability of source material from time to time. Organon contended that in the future the company might have to limit its supply. In the event, priority would be given to patients using Organon gonadotrophins. The approximate usage ratio of gonadotrophin: hCG was 10:1.

5 Letter of complaint

5.1 Letter from Organon The letter from Organon's customer services manager dated 12 December, 1996, the subject of the complaint, sought to explain some of the above-mentioned supply problems. Organon regretted that the letter did not fully explain its position.

Organon said that the letter was written after initial contact with the complainant at the hospital by the representative on or around 10 December, 1996. This resulted in a request by the representative to the customer services manager to provide a written contract proposal to the hospital, which was done in the letter.

The customer services manager correctly stated that Organon did not have sufficient quantities of urinary gonadotrophins to make them available to the community. Supplies were limited and diminishing. In view of the limited availability of Organon products, the company had found it necessary to limit supplies to those customers with whom it had contract arrangements, or to those customers who purchased its products.

The letter stated that in the event of Organon experiencing difficulty in supply of Pregnyl in the future, priority would be given to patients on Organon products and thus guarantee that any patient started on an Organon gonadotrophin would be able to complete their course.

Thus the letter laid out the company's offer to supply its products. Organon said that, as always, the customer had the choice of refusing that offer.

Organon said that no further contact was made with the hospital until March, 1997. During this time however availability of stock of urinary products continued to decline.

5.2 Conduct of the representative Organon said that during March, 1997, a telephone call was made by the hospital to the customer services manager arranging that a representative should call to discuss the proposal further. A visit was arranged, but subsequently cancelled, an alternative being offered in late April. In view of the urgency of the supply situation a visit was made by the representative on 21 March, 1997. However, she was unable to see persons responsible for agreeing the contract. She did meet with the store manager. Organon did agree to fulfil the terms of the contract as stated in the letter of 12 December although supplies or urinary gonadotrophins were becoming even more limited. Thus the representative sought urgent agreement to sign the contract.

While the representative sought to convey the urgency of the situation, Organon apologised if this was interpreted as undue pressure.

6 Conclusions

Organon said that the hospital had never chosen to purchase Organon products in preference to those of Serono, and thus the company was surprised that the trust had decided to complain to the Authority.

Sufficient quantities of urinary gonadotrophins were not available to meet the demand for treating all infertility patients. Supply of these products was restricted to those patients in clinical need of the products because they contained LH. Organon had offered to supply quantities of Puregon to the hospital. From time to time it might be necessary to limit the supply of hCG.

Since in the case of urinary gonadotrophins, recombinant FSH and hCG other similar products were available in the UK from Serono, Organon did not consider that it was in a position to compel customers to purchase its products.

Organon regretted that its conduct on this occasion had been misinterpreted by the hospital.

PANEL RULING

The Panel noted that the letter from Organon had been written in unusual and difficult circumstances. The letter stated that the urinary gonadotrophins would be directed to countries that did not have a licence for the recombinant product and that the next delivery was likely to be the company's last. Organon was the only supplier of an LH containing gonadotrophin. Given that the supply of urinary gonadotrophins could not meet the demand, there had to be some form of rationing to ensure supply for those patients who needed them. The majority of patients could be treated with an alternative, recombinant, product, which was in unlimited supply. The Panel noted that the supply of the urinary product was linked to the purchase of the recombinant product. The Panel considered that this was a reasonable approach as fertility clinics would be likely to buy across the range of products and from their total use of gonadotrophins only a small percentage would need to be urinary products, for around 1% of patients. Under the circumstances the Panel considered that it was not unreasonable to offer a limited supply of urinary gonadotrophins only to those customers who purchased other related Organon products. The Panel would not have considered it thus if the supply of urinary gonadotrophins had been unlimited or if it had been linked to Organon products unrelated to the treatment of infertility.

The Panel had some sympathy for the trust's views and could see how the actions of Organon could be misunderstood. Given the difficult circumstances, the Panel acknowledged that the solution to the problem, while not perfect, was a reasonable approach and on balance ruled no breach of Clause 18.1 of the Code.

The Panel noted that the supply situation relating to Pregnyl (hCG) was different to that of the urinary gonadotrophins. The letter stated that there had been some difficulty over the supply of Pregnyl and that, in the event of further difficulty, supplies would have to be rationed to units already using Organon products, the amount available for purchase being linked to the amount of gonadotrophin ordered. The conditions of such rationing, should it prove necessary, were set out. The Panel noted that the complainant had assumed that rationing of Pregnyl was already in effect although this was not the case. Given the circumstances the Panel considered it reasonable for Organon to alert customers to the possibility of future rationing.

The Panel noted that there was a three month gap from the time when the letter from the customer services manager had been written (December, 1996) until the representative made contact with the hospital again in March, 1997. The Panel considered that the representative's sense of urgency to get the supply agreement signed reflected the continuing decline in supply of urinary gonadotrophins. The representative was anxious to secure a supply of urinary products for the hospital. Given the circumstances the Panel ruled no breach of Clause 15.2 of the Code.

Complaint received **7 April 1997**

Case completed **3 June 1997**

LILLY v BOEHRINGER INGELHEIM AND PHARMACIA & UPJOHN

Alleged promotion of an unlicensed medicine

Lilly complained about the promotion of pramipexole, a medicine without a marketing authorization in any country, by Boehringer Ingelheim and Pharmacia & Upjohn at a symposium in London in March. Photocopies of exhibition panels were provided. In addition, a booklet containing abstracts devoted to pramipexole had been available at the joint exhibition stand. Lilly said that the statement "Pramipexole is not currently licensed in the UK" which appeared on an exhibition panel implied an expectation that a marketing authorization was anticipated.

The Panel noted that the product was not authorized in any country and considered that the status of the product in that respect could have been better explained. It did not consider that the statement "Pramipexole is not currently licensed in the UK" implied that it was licensed elsewhere or that the product would be available shortly.

In the Panel's view, where a product was not authorized anywhere a pharmaceutical company could distribute only scientific papers and information such as would be published in scientific and medical journals. A judgement had to be taken as to whether a company's activities were promotional or not. Although the Panel had some criticisms of the materials in question, it decided, on balance, that they were non-promotional. Overall the content was sufficiently scientific and the method of presentation, although on the boundary, was not considered to be promotional. No breach of the Code was ruled.

COMPLAINT

Lilly Industries Limited complained about the promotion of pramipexole by Boehringer Ingelheim Limited and Pharmacia & Upjohn Limited at the XII International Symposium on Parkinson's Disease (24 - 26 March 1997). The meeting was held in London. Lilly said that to its knowledge the product did not have a marketing authorization in any country. A breach of Clause 3.1 of the Code was alleged.

Lilly said that the joint exhibition stand for Boehringer Ingelheim and Pharmacia & Upjohn displayed several large exhibition panels devoted to pramipexole. Lilly provided three photographs of exhibition panels. The first photograph had the words "First presentation of new data on pramipexole", the second photograph had the words "Boehringer Ingelheim and Pharmacia & Upjohn are working together to develop pramipexole - a selective D_3 agonist for Parkinson's disease".

The statement "Pramipexole is not currently licensed in the UK" appeared at the bottom of both photographs. The third photograph was of two exhibition panels, the first one referring to dopamine D_3 receptors and their location within the brain. The second was headed "Symposium First presentation of new data on pramipexole - a selective D_3 agonist being developed for Parkinson's disease". The exhibition panel detailing the symposium included the statement that pramipexole was not currently licensed in the UK. Details about the Chairman, the speakers and the titles of the presentations were also provided on the exhibition panel. In addition a booklet containing abstracts, each devoted to pramipexole, from the sponsored symposium was handed out from the stand and large numbers of copies were available at the stand on all three days of the conference.

Lilly said that after making a verbal complaint, two of the exhibition panels were modified with tape. The second exhibition panel had the words "for Parkinson's disease" taped over so that it now read "Boehringer Ingelheim and Pharmacia & Upjohn are working together to develop pramipexole - a selective D_3 agonist". The exhibition panel showing the details of the symposium had the words "for Parkinson's disease" taped over in the heading although the indication was still visible on this exhibition panel as it occurred in the titles of some of the presentations. Photographs of the modifications were provided.

Lilly said that the statement "Pramipexole is not currently licensed in the UK" was displayed on the exhibition panels which, in Lilly's opinion, implied an expectation that a marketing authorization was anticipated. It was the company's understanding that a product must have an authorization somewhere in the world before any promotion could take place at an international meeting held in the UK.

RESPONSE

The complaint was taken up with both Boehringer Ingelheim Limited (Case AUTH/527/4/97) and Pharmacia & Upjohn Limited (Case AUTH/528/4/97).

Case AUTH/527/4/97

Boehringer Ingelheim said that a marketing authorization was currently not held in any country, including the UK. It contested the opinion of Lilly that the use of the word "currently" in this context implied that a marketing authorization was anticipated. It was merely a statement of the present situation. The possibility of a marketing authorization at some time in the future could not be excluded.

The purpose of the exhibition was to inform the attendees, who were all specialists in the management of Parkinson's disease, of the current status in the clinical research into the use of pramipexole, a selective D_3 agonist, in this condition. To facilitate the information exchange, a booklet containing abstracts of presentations from a recently sponsored symposium concerning pramipexole was made available at the stand for those doctors who wanted it.

After the initial verbal complaint at the stand, the modifications to the exhibit were made as indicated by Lilly. In particular, although the doctors present at the

meeting probably knew that pramipexole was not licensed in the UK, it was thought desirable to emphasise this point in the light of the complaint.

As further emphasis to the non-promotional but informative nature of the exhibit, it should be noted that the brand name was not given.

Boehringer Ingelheim submitted that the purpose of the exhibition was to provide the latest research information to a highly selected group of doctors many of whom had been involved in the clinical trials programme with pramipexole and who were very knowledgeable on all aspects of Parkinson's disease and was therefore not to promote the prescription, supply, sale or administration of pramipexole.

Boehringer Ingelheim concluded that the exhibition was not promotion as defined in the Code. Copies of the materials made available at the stand were provided.

Case AUTH/528/4/97

Pharmacia & Upjohn said that pramipexole was a compound under development for Parkinson's disease. Boehringer Ingelheim and Pharmacia & Upjohn were working together to develop it further as a potential treatment for patients with the disease. There were ongoing negotiations between the two companies' head offices in Germany and the US where details of the collaboration were still to be agreed. Pharmacia & Upjohn referred to the response made by its colleagues at Boehringer Ingelheim UK.

PANEL RULING

The Panel noted that international meetings held in the UK were subject to the UK Code. Companies operating in the UK were responsible under the Code for activities in the UK of their overseas parents and affiliates.

The Panel examined the materials provided at the meeting by Boehringer Ingelheim and Pharmacia & Upjohn. The exhibition stand had included two current concept booklets. One entitled "Dopamine Research: Its Potential Clinical Significance" was written by a professor of pharmacology, and two Upjohn research scientists. The second booklet entitled "Parkinson's Disease and Related Neurodegenerative Disorders" was written by a professor of neurology. The programme was provided for the symposium on the afternoon of 25 March.

It was a two hour meeting with four presentations, a discussion and a question and answer session. An abstract for each of the four presentations was provided. The materials for the symposium appeared in a folder headed "Scientific" followed by the statement in facsimile handwriting "Towards a New Paradigm in the Treatment of Parkinson's Disease". Boehringer Ingelheim also supplied disks labelled "XIIth International Symposium on Parkinson's Disease" followed by "Abstracts-On- Disk made possible through an educational grant from ... Boehringer Ingelheim" and a CD ROM, "Digital Humans".

The Panel noted that pramipexole was not licensed in any country. It considered that the licensing status of the product could have been explained more clearly. It did not accept, however, that the use of the phrase "Pramipexole is not currently licensed in the UK" implied that the product was licensed somewhere else or that the product would be available shortly.

The Panel examined the requirements of Clause 3 of the Code together with its supplementary information.

The supplementary information to Clause 3 headed "Promotion at international conferences" did not apply as pramipexole was not licensed anywhere in the world. The supplementary information headed "Marketing Authorization" stated that "The legitimate exchange of medical and scientific information during the development of a medicine is not prohibited provided that such information or activity does not constitute promotion which is prohibited under this or any other clause". In the Panel's view, a company could distribute scientific papers and information such as would be published in scientific and professional journals on unlicensed products/indications at an international meeting of high scientific standing. A judgement had to be made as to whether the activities were promotional or not.

Turning to the information provided by Boehringer Ingelheim and Pharmacia & Upjohn at the exhibition stand at the international meeting, the Panel considered that the title of the symposium "Towards a New Paradigm in the Treatment of Parkinson's Disease", and the repeated use of the facsimile hand-written title on the materials associated with the symposium, might be open to criticism. The abstracts were typewritten pages on plain, non glossy paper with limited use of colours and emboldening. They did not have the appearance of promotional material. The Panel had no way of assessing whether the abstracts were a fair reflection of the symposium. Overall the Panel considered that the content and presentation of the abstracts was scientific and non promotional and that the exhibition panels were not unreasonable.

The Panel did not think it was unacceptable for attendees at the meeting to receive the abstracts etc even if they had not been present at the sponsored symposium.

Although the Panel had some criticisms about the material, it decided that, on balance, the material was non promotional. Overall the content was sufficiently scientific and the method of presentation, although on the boundary, was not considered to be promotional. Attendees at the exhibition would be experts in the field. The Panel ruled no breach of the Clause 3 of the Code. This ruling applied to both companies.

The Panel noted that its ruling applied to the use of the materials at the international symposium in question. Use of the same materials in other ways could be in breach of the Code.

The Panel queried a prize given in a competition at the meeting. There were no details about the actual competition but the prize offered was a London "Eyewitness" guide. The companies should be reminded that competitions at international exhibitions held in the UK needed to comply with the UK Code. The questions had to be a *bona fide* test of skill and recognise the professional standing of the recipients and the prizes had to be relevant to the potential recipient's work and not out of proportion to the skill required in the competition. The

Panel considered that a London "Eyewitness" guide was not relevant to the practice of the professionals entering the competition as required by Clause 18.1. The Panel requested that its concerns be drawn to the attention of Boehringer Ingelheim and Pharmacia & Upjohn.

Complaint received 8 April 1997

Cases completed 5 June 1997

CASES AUTH/529/4/97 & AUTH/530/4/97

LILLY v ORION AND NOVARTIS

Promotion of entacapone

Lilly alleged that entacapone, a product which did not have a marketing authorization in any country, had been promoted by Orion Pharma and Novartis at a symposium in London in March. Photocopies of exhibition panels were provided. Clinical papers and a glossy brochure had been made available on the Orion/Novartis stand.

The Panel observed that when a product was not authorised anywhere, then any information made available must be such as would be published in scientific and professional journals and be provided in connection with the legitimate exchange of medical scientific information during the development of a medicine as was permitted by the Code. Although some of the materials were acceptable, others were not as they were considered to be of a promotional nature. The Panel considered that Orion and Novartis had promoted entacapone prior to it receiving a marketing authorization and ruled that there had been a breach of the Code.

COMPLAINT

Lilly Industries Limited complained about the promotion of entacapone by Orion Pharma and Novartis at the XII International Symposium on Parkinson's Disease (24 - 26 March 1997). The meeting was held in London. Lilly said that, to its knowledge the product did not have a marketing authorization in any country. A breach of Clause 3.1 of the Code was alleged.

Lilly said that the Orion/Novartis stand displayed several posters promoting entacapone. Three photographs were provided. The first photograph showed two exhibition panels. One referred to an Orion symposium and the other, which was also the subject of the second photograph, showed an exhibition panel which was headed "Enter a new dimension in the treatment of Parkinson's disease". It included a statement that the product was not licensed in the UK. Both exhibition panels had Orion's name on but the second panel also had Novartis on it. The third photograph showed an exhibition panel with a couple sitting on a bench underneath an umbrella with the words "entacapone a COMT inhibitor" followed by "Orion" and the statement "Entacapone does not have a licence in the UK". In addition clinical papers on entacapone were available without request at the stand as well as issues of a publication entitled "Entacapone news". Lilly said that these, and an A3 glossy brochure containing abstracts on entacapone from an Orion sponsored symposium, were clearly promotional in style and content and available at the exhibition stand for all three days of the conference.

Lilly said that after a verbal complaint the word "entacapone" was covered with tape on the exhibition panel on which Novartis was named although it was still visible at the lower part where it stated that entacapone did not have a licence in the UK. The Orion exhibition panels remained however as did the materials described above.

RESPONSE

The complaint was taken up with both Orion Pharma (UK) Ltd (Case AUTH/529/4/97), and Novartis Pharmaceuticals UK Ltd (Case AUTH/530/4/97).

CASE AUTH/529/4/97

Orion said that entacapone was a product of Orion Research and Development. There was a worldwide licence, supply and distribution agreement between Orion and Novartis which provided for different arrangements in different countries. For the XII International Symposium on Parkinson's Disease, the international groups from the two companies developed a joint presentation for entacapone. Orion Pharma UK and Novartis Pharmaceuticals UK were similarly developing a working relationship and operating procedures in the UK for entacapone.

The involvement of the two UK companies in developing the material for the international symposium differed. Orion rather than Novartis was therefore responding in terms of the material presented.

Orion said that entacapone did not have licence anywhere in the world and at the time of the meeting no licence application had been made. Orion submitted that the information provided was a legitimate exchange of medical and scientific information allowed for during the development of entacapone and was not promotional. Attention was drawn to the supplementary information to Clause 3 of the Code.

Orion submitted that the availability of entacapone was restricted to approved clinical research studies. It had not been provided on a named patient basis or indeed on any other basis outside of clinical studies despite requests. The fact that the scientific material made it clear that the product was not licensed in the UK and the fact that the product was not available outside of approved studies demonstrated that the activity was not promoting the prescription, supply or sale of entacapone. Under Clause 1.2 Orion's activities did not therefore fit the definition of

promotion.

Orion said that catechol O-methyltransferase (COMT) inhibitors were a new class of product being developed to assist in the management of patients with Parkinson's disease. Tolcapone from Roche and entacapone were the most advanced COMT inhibitors in development. No COMT inhibitor had been marketed to date within the EU. Tolcapone had been licensed in Switzerland within the last two months. As a new class of product COMT inhibitors had generated substantial interest from the medical profession during their development with the latest medical and scientific information being in demand.

Orion said at the time of the verbal complaint from the Lilly staff it contacted the Medicines Control Agency for advice on materials that could be presented at an international symposium when the product did not have UK licence. The company reviewed the available material and took action reflecting this advice. For example, indicating that entacapone did not have a licence in the UK. The action taken did not satisfy the Lilly employee but at no time had Orion been contacted by management from Lilly to discuss the matter. The company went on to deal with each piece of the material in question.

1 Exhibition Panel 1 - Symposium advertisement

As part of the main symposium a satellite symposium had been sponsored by Orion International and Orion Research and Development. An international group of speakers would be presenting on the management of patients with Parkinson's disease discussing COMT inhibition and sharing clinical data. The exhibition panel simply advertised the symposium details.

A change was made to the exhibition panel on the day following discussion with the manager from Lilly in order to try to reach a satisfactory compromise. The change involved covering the words "of Parkinson's disease" from the title of the symposium "Entacapone - a novel COMT-inhibitor in the treatment of Parkinson's disease". Orion said that the change was unsatisfactory as far as it was concerned at the time and in hindsight believed it was unnecessary.

2 Exhibition Panel 2 - Principles of COMT inhibition

The exhibition panel was headed "Enter a new dimension in the treatment of Parkinson's Disease" with the subheading "Principles of COMT inhibition".

Orion said that this was a presentation of scientific and medical information. COMT inhibitors modified the metabolism of levodopa, hence levodopa had to be part of the science when presenting the principles of COMT inhibition.

The sentence "Rationale for co-administration of entacapone and levodopa" was changed to "Rationale for co-administration" in order to avoid linking entacapone to the presentation. The addition of the statement concerning the licence status of entacapone possibly negated any value in taking this action but by doing so ensured there was no misinterpretation as to the availability of the product.

3 Exhibition Panel 3 - Picture

The exhibition panel was a picture of a couple sitting on a bench under an umbrella. The statement "entacapone a COMT inhibitor" appeared beneath the picture. Orion had added the statement "Entacapone does not have a licence in the UK".

Orion did not see a problem with this panel. The licence statement was added as per its interpretation of the Medicines Control Agency's advice.

4 Entacapone News, Issues 2 & 3

Entacapone News issue 2 was dated September 1995 and issue 3 was dated January 1997. Orion's name was given on both issues.

Orion said that published in line with the development of entacapone these publications provided medical and scientific information on COMT inhibitors in general and entacapone in particular. Issue two reviewed published information concerning clinical applications. Issue three reported on an Orion Pharma International and Orion Research and Development sponsored symposium from the 4th International Congress of Movement Disorders (Vienna, June 17-21 1996). In both cases the printed material was reviewed and approved by the speakers thus ensuring that it accurately reflected their presentations.

5 Entacapone A novel COMT inhibitor in the treatment of Parkinson's Disease

This item was a four page A3 publication.

The item covered the presentation from the Orion sponsored satellite symposia held on 24 March 1997 during the International Conference. The item was not available until after the symposium had been held. As with Entacapone News it was reviewed and approved by the speakers thus ensuring it accurately reflected their presentation.

6 Published papers

Available on the stand were two published papers, one from the European Journal of Neurology and the other from Neurology.

Orion submitted that items 4, 5 and 6 provided medical and scientific information that might be legitimately exchanged during the development of a medicine.

Orion said that the individual items were provided in response to specific requests. There was no proactive distribution of the material. Orion submitted that the product was at the final stages of development in some part of the world and just prior to licence application but this stage had not been completed. The timing supported its claim that the information provided and the manner in which it was provided was a legitimate exchange of medical and scientific information allowed during the development of a product.

CASE AUTH/530/4/97

Novartis Pharmaceuticals UK Ltd was surprised to receive the formal complaint since it was aware that its

colleagues from Orion had entered into extensive communications with a Lilly representative in an attempt to address the concerns raised.

The company said that entacapone was a product of Orion Research and Development which had not to date been licensed anywhere in the world. An agreement for the world-wide supply and distribution of entacapone had been formulated between Novartis and Orion. For the international symposium in question the international groups from both companies developed a joint presence for entacapone including the provision of scientific data and the exhibition panels referred to by Lilly. Unfortunately the material had not been subject to Code of Practice review by Novartis UK and had been presented without the prior knowledge of the UK company.

As part of a series of standard operating procedures being developed by the two companies, steps would be taken to avoid any repetition of this lack of input and to ensure that all materials used at international meetings in the UK would be subject to the same level of scrutiny as those produced by both the UK companies.

The materials used at the meeting were produced by the Orion and Novartis international groups.

PANEL RULING

The Panel was concerned that Novartis in the UK had not seen the materials that had been made available by Novartis on the joint exhibition stand with Orion. International meetings held in the UK were subject to the UK Code. Companies operating in the UK were responsible under the Code of Practice for activities in the UK of their overseas parents and affiliates.

The Panel examined the materials provided at the meeting by Orion and Novartis as detailed in the Orion response.

The Panel noted that entacapone was not licensed in any country. It considered that the licensing status of the product could have been explained more clearly. The Panel noted that Orion had taken advice from the Medicines Control Agency about the materials.

The Panel examined the requirements of Clause 3 of the Code together with its supplementary information.

The supplementary information to Clause 3 headed "Promotion at international conferences" did not apply as entacapone was not licensed anywhere in the world. The supplementary information headed "Marketing Authorization" stated that "The legitimate exchange of medical and scientific information during the development of a medicine is not prohibited provided that such information or activity does not constitute promotion which is prohibited under this or any other clause". In the Panel's view a company could distribute scientific papers and information such as would be published in scientific and professional journals on unlicensed products/indications at an international meeting of high scientific standing. A judgement had to be made as to whether the activities were promotional or not.

The Panel then examined the information provided by Orion and Novartis on the exhibition stand at the international meeting.

The Panel considered that the exhibition panel advertising the symposium (item 1 above) was on the limits of acceptability. The title of the symposium "Entacapone - a novel COMT-inhibitor in the treatment of Parkinson's disease" might be seen as a promotional statement rather than a scientific statement.

The Panel considered that the exhibition panel headed "Enter a new dimension in the treatment of Parkinson's disease" (item 2 above) had the appearance of promotional material. It was very similar in style to a journal advertisement and promotional claims such as "Easy for patient and physician" were made for the rationale of co-administering entacapone and levodopa. Similarly the Panel considered that the exhibition panel 3 (item 3 above) also had the appearance of promotional material rather than scientific information.

The Panel considered that the Entacapone News issues (item 4 above) did not fit the criteria that a company could distribute scientific papers and information such as would be published in scientific and professional journals. They were glossy publications with promotional statements used as headings to various sections for example "Entacapone - an efficient levodopa extender". The material had the appearance of promotional material. The September 1995 issue (issue 2) referred to clinical applications of entacapone and included "selected abstracts". The Panel did not know the basis of the selection of the abstracts. The January 1997 issue (issue 3) reported on a conference held in Vienna in 1996.

The Panel noted with regard to the A3 publication headed "Entacapone A Novel COMT Inhibitor in the Treatment of Parkinson's Disease" (item 5 above) that it was acceptable to send a non promotional symposium report which discussed unlicensed medicines and/or indications to people who had attended that meeting. If such a report was sent to others, it would be in breach of the Code. The Panel noted that each page was headed "Entacapone - A novel COMT inhibitor in the treatment of Parkinson's Disease" which it considered was a promotional statement inappropriate for a scientific item. The Panel had no way of assessing whether the information was a fair reflection of the symposium. The Panel was concerned that the material did state that entacapone was "... a very safe drug in use with levodopa and/or other conventional anti-Parkinson drugs". Unqualified use of the word "safe" was not permissible. On balance the Panel considered that the publication was on the limits of acceptability regarding its content and presentation.

The Panel considered that it was acceptable to distribute the published papers (item 6 above) at the exhibition stand.

The Panel considered that as some of the materials were promotional they were not within the supplementary information to Clause 3 regarding the legitimate exchange of medical and scientific information during the development of a medicine. The Panel considered that Orion and Novartis had promoted entacapone prior to it receiving a marketing authorization. The Panel therefore ruled a breach of Clause 3.1 of the Code. This ruling applied to both companies.

Complaint received 8 April 1997

Cases completed 3 June 1997

CASE AUTH/533/4/97

NO BREACH OF THE CODE

RHÔNE-POULENC RORER v SCHERING-PLOUGH

Promotion of Nasonex

Rhône-Poulenc Rorer alleged that Schering-Plough had promoted Nasonex, an unlicensed medicine, to general practitioners attending a postgraduate meeting at a hospital.

The Panel noted that there was a conflict of evidence in this case but considered that there was no evidence that the representative involved had promoted Nasonex or that promotional material for it had been supplied. No breach of the Code was ruled.

COMPLAINT

Rhône-Poulenc Rorer Limited submitted a complaint regarding the activities of Schering-Plough Ltd in relation to its unlicensed product Nasonex. Rhône-Poulenc Rorer alleged that at a postgraduate meeting at a named district hospital on 18 March, 1997, Schering-Plough actively promoted Nasonex to general practitioners using photocopied promotional materials. Breaches of Clauses 3.1 and 3.2 of the Code were alleged.

RESPONSE

Schering-Plough said that Nasonex had received a product licence on 10 April 1997 and was therefore not licensed at the time of the postgraduate meeting in question. Therefore no Nasonex promotional materials were supplied to the representative attending that meeting.

The company believed that there was a telephone conversation between the medical directors of Schering-Plough and Rhône-Poulenc Rorer in which the allegations were discussed and, before the allegations were discussed with the representative concerned, a letter was sent to the sales force reinforcing correct procedure. A copy of the letter dated 4 April 1997 and signed by the national sales manager, was provided. In subsequent conversations with the representative in question, the representative maintained that the discussion on Nasonex was initiated by a general practitioner. Schering-Plough had reassured Rhône-Poulenc Rorer that if, indeed, an offence was committed it would ensure that it did not happen again. If Rhône-Poulenc Rorer could provide evidence that the representatives did behave in the manner alleged, then the company would take appropriate disciplinary action. In the meantime, the company submitted there was no case to answer.

PANEL RULING

The Panel noted that there was a conflict of evidence. Rhône-Poulenc Rorer alleged that the representative had promoted Nasonex to a general practitioner and that photocopies of promotional material had been used. Schering-Plough said that the discussion was initiated by the general practitioner and that no promotional material was supplied to the representative in question.

The Panel noted that it was difficult in cases concerning discussions between a representative and a general practitioner to know what had been said, especially in this case where the complaint had come from a third party, Rhône-Poulenc Rorer. There was no evidence that the representative had promoted Nasonex and nor was there any evidence that promotional material for Nasonex had been supplied. The Panel therefore ruled no breach of Clause 3 of the Code.

During its consideration of this case the Panel was concerned about the letter dated 4 April 1997 sent by the Schering-Plough national sales manager to the sales force. The letter read:-

"It has come to my attention that a representative has been detailing Nasonex to a number of GPs at a group event. May I remind everyone that Nasonex cannot be detailed to any customer audience until written confirmation of a licence being granted has been received by the company, unless the discussion is initiated by the doctor/pharmacist etc. Under no circumstances should you be pro-actively discussing Nasonex and making product claims about it or how it compares to any competitors until such a licence has been granted or you are asked about the product. To do so is illegal and could jeopardise a licence being granted."

In the Panel's view this instruction suggested that Schering-Plough might have pushed the boundary too far in relation to responding to specific enquiries from healthcare professionals. Clause 1.2 of the Code exempted from the requirements of the Code replies made in response to individual enquiries from members of the health professions. Such replies were exempt only if they related solely to the subject matter of the enquiry and were not promotional in nature. An enquiry from a general practitioner about an unlicensed product was not an opening for the company to tell that enquirer everything about the product. The company must limit its response to answering the specific question. In the Panel's view it was advisable for such enquiries to be dealt with by the company's medical or medical information departments. The letter implied that once a doctor had asked about Nasonex, representatives were free to "detail" the product. This would not be acceptable under the Code. The Panel requested that Schering-Plough be reminded of its responsibilities in this area.

Complaint received **16 April 1997**

Case completed **20 May 1997**

CASE AUTH/534/4/97

SCHERING HEALTH CARE v GUERBET

Newsletter and Internet entry referring to Endorem and Xenetix

Schering Health Care complained about a Guerbet newsletter and Internet pages referring to Endorem and Xenetix. It was alleged that neither provided prescribing information for the products though therapeutic indications had been given.

The Panel considered that the newsletter was promotional and should have included prescribing information. Similarly, the Internet information was promotional and access to the prescribing information should have been provided. Breaches of the Code were ruled in both instances.

COMPLAINT

Schering Health Care Limited complained about a newsletter and Web pages on the Internet used by Guerbet Laboratories Ltd in relation to its products Endorem and Xenetix. Guerbet Laboratories was not a member of the ABPI but agreed to comply with the Code.

Schering pointed out that products were named in both items and therapeutic indications were given, but no prescribing information was supplied. Breaches of Clause 4 of the Code were alleged.

The newsletter was entitled "Contrasts" and was dated Autumn 1996. The newsletter referred to Endorem as the first liver specific MRI agent. Detailed information about the product and its use was provided in the newsletter. The newsletter gave information about the company in the UK as well as events, literature services etc. The newsletter briefly referred to Xenetix, a non ionic contrast medium.

Schering Health Care had provided print-outs from the Guerbet home page. It referred to Endorem as a superparamagnetic contrast agent, which offered improved MRI imaging of focal lesions of the liver. Access to other information, including the newsletter, was referred to on the home page.

RESPONSE

Guerbet submitted that the aim of the newsletter was to provide a general overview of what was happening in the imaging community and within the company. It was directly mailed to UK radiologists and radiology business managers. It was also made available at specialist meetings. Three thousand copies were printed and the remaining few were being held awaiting the views of the Authority.

Guerbet said that the Web page had been withdrawn and would be amended to meet the guidelines issued in the Code of Practice Review May 1996. Initially the pages were accessible to all. The new page would contain basic information for general consumption with access to selected groups (doctors, radiographers and pharmacists) via codes distributed on request from Guerbet.

PANEL RULING

The Panel examined the newsletter and considered that it was promotional. It included claims for the products Endorem and Xenetix and prescribing information was thus required. The Panel therefore ruled a breach of Clause 4.1 of the Code.

The Panel did not examine the text of the newsletter. It considered that Guerbet would be well advised to review the newsletter to ensure that it complied with all the relevant requirements of the Code.

The Panel noted that this was the first complaint about information on the Internet. The Authority had issued guidance in the May 1996 Code of Practice Review. The guidance was likely to be updated during 1997. The Internet presented difficulties for the Authority in relation to the requirements of the Code. The Panel noted that Guerbet intended to restrict access to information in the future. The Panel considered that the information provided on the Web site was promotional and access to the prescribing information should have been provided. The Panel therefore ruled a breach of Clause 4.1 of the Code.

Complaint received **18 April 1997**

Case completed **28 May 1997**

CASE AUTH/538/5/97

CONSULTANT PHYSICIAN v BAYER

Letter on Lipobay

A consultant physician complained that a "Dear Doctor" letter sent by Bayer in relation to Lipobay was in breach of the Code because it failed to include the non-proprietary name adjacent to the most prominent display of the brand name.

The Panel ruled that there had been a breach of the Code.

COMPLAINT

A consultant physician complained that a "Dear Doctor" letter about Lipobay, which had been sent to him by Bayer plc Pharmaceutical Division, failed to display the approved name adjacent to the most prominent display of the brand name in breach of Clause 4.2 of the Code.

The complainant had sent a copy of his letter of complaint to Bayer.

RESPONSE

Bayer said that the letter had been sent to all general practitioners, hospital doctors and pharmacists (retail and hospital) on its mailing list. When the company received the copy of the complainant's letter all further promotional letters were stopped from being distributed.

Bayer apologised for the breach. The company was reviewing the proofs to ascertain how this oversight had occurred so that it could amend its procedures accordingly in order that it did not occur again. Bayer contended that this was a genuine oversight which it would take all steps to avoid in future.

PANEL RULING

The Panel noted that the "Dear Doctor" letter contained numerous references to Lipobay and that the brand name appeared in logo type in the top right hand corner. The only reference to cervistatin, the non-proprietary name, was in the prescribing information printed on the back of the letter. 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 this Clause and not of Clause 4.2. The failure to include the non-proprietary name immediately adjacent to the most prominent display of the brand name meant that Bayer had not complied with Clause 4.1. The Panel therefore ruled a breach of Clause 4.1 of the Code.

Complaint received **6 May 1997**

Case completed **4 June 1997**

CASE AUTH/539/5/97 *NO BREACH OF THE CODE*

NOVO NORDISK v SCHERING HEALTH CARE

Nuvelle TS abbreviated advertisement

Novo Nordisk complained about an illustration of a naked woman in a shower which was used in an advertisement for Nuvelle TS issued by Schering Health Care. The Panel did not consider that the illustration was unacceptable. No breach of the Code was ruled.

COMPLAINT

Novo Nordisk Pharmaceuticals Ltd complained about an abbreviated advertisement for Nuvelle TS (a transdermal hormone replacement therapy (HRT) patch) issued by Schering Health Care Limited. The advertisement appeared in MIMS, March 1997. The illustration was of the torso of a naked woman in the shower.

Novo Nordisk said that there was no evidence in the text of the advertisement to support Schering's view that the image of a naked woman had been used with the purpose of showing the unobtrusive nature of the patch and that adhesion was effective in the shower. Novo Nordisk therefore concluded that the image was used for the purpose of attracting attention to the material. A breach of Clause 9.1 of the Code was alleged.

RESPONSE

Schering Health Care submitted that the imagery used was certainly not intended merely to attract attention to the advertisement; it had the entirely legitimate aim of conveying messages in a manner which was clearer and more concise than could be achieved in written form. Schering Health Care believed that prescribers were likely to be more convinced of the unobtrusive nature of the patch by the message being visual rather than verbal. In addition, the well recognised adhesion problems with patches were addressed in the material by locating the woman in a shower.

As Clause 9.1 raised issues of suitability and taste, which, by their nature, were subjective, the company pointed out

that no complaints from any other source had been received.

RULING

The Panel examined the material. The illustration was of the torso of a woman, almost in silhouette, taking a shower. The Panel did not consider that the illustration was unacceptable. It was low key and relevant to the product which was a patch to be worn for three to four days at a time. No breach of Clause 9.1 of the Code was ruled.

Complaint received 6 May 1997

Case completed 6 June 1997

CASE AUTH/542/5/97

DIRECTOR/PARAGRAPH 16 v SANDOZ

Disposable camera given as a promotional aid

During the consideration of another complaint, the Code of Practice Panel queried whether the gift of a disposable camera as a promotional aid was acceptable as being relevant to the practice of medicine and decided that the matter should be taken up with Sandoz.

The Panel noted that the camera was said to be to enable the production of photographs to assist with diagnostic work, particularly in relation to skin conditions. The instructions on the camera, however, stated that it was to take pictures in daylight only, that indoor pictures were not recommended and that the photographer had to stay more than one metre from the subject.

The Panel did not consider that such a camera was relevant to the practice of medicine and ruled there had been a breach of the Code.

COMPLAINT

This case arose from a previous matter (Case AUTH/522/4/97) in which the Panel had identified an apparent breach of Clause 18.1 of the Code relating to the provision of a disposable camera as a promotional aid for Lamisil. The matter was taken up with Sandoz under Paragraph 16 of the Constitution and Procedure. The Panel had queried whether a disposable camera was relevant to the practice of medicine.

RESPONSE

Sandoz said that consideration was given to the suitability of a disposable camera as a promotional aid before approval was granted for its use. It was apparent from the company's investigations that such a camera could produce photographs of sufficient quality to assist with diagnostic work, particularly in relation to skin conditions. The company provided a photocopy of photographs taken with the disposable camera in a well lit room which demonstrated that it was possible to use such an item to monitor the outcome of a treatment course of therapy, the course of an unexpected skin reaction, or even as a means of recording patient symptoms for specialist consideration. The original mailing offering the item made reference to the use of the camera for just such a purpose in monitoring the outcome of a treatment course of Lamisil tablets. A disposable camera was supplied.

RULING

The Panel noted that the disposable camera cost £3.62. The camera provided 27 exposures. The instructions on the back of the camera said that it was to take outdoor pictures in daylight only and indoor pictures were not recommended. Photographers were advised to stay more than one metre from the subject.

The Panel noted that the mailing offering the disposable camera stated that "recipients could record success with Lamisil tablets particularly in dermatophyte skin infections". The complainant in Case AUTH/522/97, a general practitioner, had stated that he was going to give the camera to his children.

The Panel noted that Clause 18.2 of the Code stated that gifts in the form of promotional aids, whether related to a particular product or of general utility, could be distributed to members of the health professions, provided that such gifts were inexpensive and relevant to the practice of their profession. Inexpensive was defined as costing a company no more than £5 excluding VAT. The Panel noted that the disposable camera was acceptable on the grounds of cost as it had cost the company £3.62.

The Panel examined the photocopy of photographs provided by Sandoz. The camera had recorded marks on the skin of a patient. In the Panel's view it would be difficult to take good quality close ups of skin conditions in the surgery, as, according to the instructions printed on the back of the camera, the photographer was advised to stand more than one metre away from the subject and to use the camera outdoors. The Panel did not accept that the disposable camera as provided by Sandoz was relevant to the practice of medicine and therefore ruled a breach of Clause 18.1 of the Code.

Proceedings commenced 22 April 1997

Case completed 3 June 1997

CASE AUTH/549/5/97

NO BREACH OF THE CODE

GENERAL PRACTITIONER v HOECHST MARION ROUSSEL

Telfast journal advertisement

A general practitioner alleged that the illustration of pigs with wings in a Telfast journal advertisement issued by Hoechst Marion Roussel was offensive and insulting to the Muslim and Jewish communities. The Panel considered that the advertisement was not unreasonable in relation to the requirements of the Code that material must not be likely to cause offence and that high standards must be maintained. No breach of the Code was ruled.

The advertisement in question was one for Telfast issued by Hoechst Marion Roussel (ref TEF024A). The illustration for the advertisement was of pigs with wings. It was headed "The impossible can happen - we've improved on Triludan (terfenadine)".

COMPLAINT

A general practitioner alleged that the advertisement was offensive and insulting to the Muslim and Jewish communities.

The complainant said that there were millions of doctors and Muslim patients living in this country who did not eat pig or any pig products as it was against their religion. There were other communities, ie Jewish and vegetarian, who did not eat pig or pig products. The complainant had discussed the matter with the managing director of Hoechst Marion Roussel and, as the company had failed to take any action, the complainant brought it to the Authority's attention so that it might ask Hoechst Marion Roussel to withdraw it and make a public apology.

RESPONSE

Hoechst Marion Roussel Ltd said that it had not set out to offend or insult the intended audience with the advertisement and therefore the offence was not perpetrated by it, but was more in the eye of the beholder. Nevertheless, it recognised that the customer was always right and so were the customer's perceptions. The company therefore apologised if, by default, it had offended the complainant.

In the context of Clause 9.1 of the Code the company was well aware of the general symbolism, sensitivities and taboos of all the ethnic, religious and social groups of its customer base; these were mostly also represented amongst its own employees. The company's advertisements were tested against this background before release.

To respond to the complainant fully, however, it was necessary to go further. The following quotation from *"Through the Looking-Glass"*,

> *'The time has come,' the Walrus said,*
> *'To talk of many things:*
> *Of shoes - and ships - and sealing wax -*
> *Of cabbages - and kings -*
> *And why the sea is boiling hot -*
> *And whether pigs have wings.',*

was by one of this country's greatest writers read by children and indeed people of all ages. It set in the literary context the concept of whether pigs might fly, and if they did whether this might represent something quite remarkable.

For this reason the company had taken the well-worn saying "pigs might fly" to represent the genuine progress that had been proved to have been made by the development of fexofenadine (Telfast 120) to improve on terfenadine (Triludan). As the active metabolite of terfenadine, fexofenadine, was devoid of the interactions which led to cardiac arrythmias now attributed to terfenadine when not used according to its labelling, Telfast 120 was an advance on a medicine which itself was a substantial breakthrough in the development of antihistamines.

The flying pig motif represented an abstract concept intended to place this medical advance in a well-understood and accepted British cultural context. It did not represent either Triludan or Telfast; it was not a religious symbol; it was not intended to be eaten.

Hoechst Marion Roussel submitted that the pig had an important part in the economic and cultural heritage of this and many other countries. It was indeed eaten, as bacon, ham or pork, by some but not all citizens. It was a significant contributor to the agricultural economy both in the food chain and through exports; it provided many farmers with their livelihood. Over the centuries this important animal had contributed to the folk culture of this country which was shared by most who were born or came to live here.

The pig was part of literature and of art through paintings and prints from a number of well-known artists. More recently it had been at the centre of at least two award-winning films, namely "A Private Function" and "Babe".

The pig was well represented in the English language, the origins of which went back centuries. Children wore their hair in pig-tails, owned piggy-banks, and played piggy-in-the-middle. Of course, as with many concepts, the positive and acceptable were offset by images of opprobrium, thus 'to buy a pig in a poke', 'to make a pig's ear of something', 'to make a pig of oneself' or 'to sweat like a pig'.

The company's view was that the complainant was demonstrating a degree of intolerance of the culture in which he found himself. The complainant, in the interest of his patients, must interpret with equanimity the many presentations of the living world.

Finally, Hoechst Marion Roussel referred to a quotation from Shakespeare:

'Some men there are love not a gaping pig;
Some, that are mad if they behold a cat;
And others, when the bagpipe sings i' the nose,
Cannot contain their urine.'

RULING

The Panel considered that the advertisement was a light-hearted play on words referring to the well used saying that "pigs might fly". It was unfortunate that the complainant had found the advertisement offensive and insulting. This view would not be shared by the majority of the audience.

The Panel considered that the advertisement was not unreasonable in relation to the requirements of Clause 9.1 of the Code which stated that material must not be likely to cause offence and that high standards must be maintained. The Panel therefore ruled no breach of Clause 9.1 of the Code.

Complaint received **15 May 1997**

Case completed **4 June 1997**

CODE OF PRACTICE REVIEW - AUGUST 1997

Cases in which a breach of the Code was ruled are indexed in **bold** type.

448/7/96	**Lorex Synthélabo v Yamanouchi**	**Promotion of Flomax**	**Breach 4.1, 7.2 & 7.8**	**Appeal by respondent**
481/12/96	CCLpk v Leo	Use of treatment protocol	No breach	No appeal
486/1/97	**Consultant Dermatologist v Wyeth**	**Letter on Minocin**	**Breach 2, 9.1 & 10.1**	**Appeal by respondent**
492/1/97	**Yamanouchi v Lorex Synthélabo**	**Promotion of Xatral**	**Breach 7.2, 7.3, 7.8 & 18.1**	**No appeal**
493/1/97	**Clinician v Serono**	**Curosurf mailing**	**Breach 7.2**	**Appeal by complainant**
498/2/97	Consultant Psychiatrist v Bristol-Myers Squibb	Sponsored self help booklet	No breach	No appeal
500/2/97 to 511/2/97	General Practitioner v twelve companies	Sponsorship of meetings	No breach	No appeal
512/2/97	**Glaxo Wellcome v Geigy**	**Foradil detail aid**	**Breach 7.6**	**No appeal**
513/2/97	**Sandoz v Fujisawa**	**Letter on Prograf**	**Breach 7.2**	**No appeal**
516/3/97	General Practitioner v Sandoz	Disease area campaign to public	No breach	Appeal by complainant
520/3/97	**Clinician v Serono**	**Curosurf contract letter**	**Breach 15.3**	**No appeal**
521/3/97	**Director v Ciba**	**Breach of undertaking**	**Breach 2 & 21**	**No Appeal**
522/4/97	**General Practitioner v Sandoz**	**Supply of promotional aid**	**Breach 15.3**	**No appeal**
523/4/97	**Dermal v Panpharma**	**Promotion of Movelat**	**Breach 7.2 & 7.10**	**No appeal**
524/4/97	Drug & Therapeutics Committee v Organon	Puregon purchase agreement	No breach	No appeal
527/4/97 & 528/4/97	Lilly v Boehringer Ingelheim & Pharmacia and Upjohn	Information on pramipexole	No breach	No appeal
529/4/97 & 530/4/97	**Lilly v Orion & Novartis**	**Promotion of entacapone**	**Breach 3.1**	**No appeal**
533/4/97	Rhône-Poulenc Rorer v Schering Plough	Promotion of Nasonex	No breach	No appeal
534/4/97	**Schering Health Care v Guerbet**	**Newsletter and Internet entry referring to Endorem and Xenetix**	**Breach 4.1**	**No appeal**
538/5/97	**Consultant Physician v Bayer**	**Letter on Lipobay**	**Breach 4.1**	**No appeal**
539/5/97	Novo Nordisk v Schering Health Care	Nuvelle TS abbreviated advertisement	No breach	No appeal
542/5/97	**Director/Paragraph 16 v Sandoz**	**Disposable camera as promotional aid**	**Breach 18.1**	**No appeal**
548/5/97	General Practitioner v Hoechst Marion Roussel	Telfast journal advertisement	No breach	No appeal

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 for promotional purposes
- the sponsorship of promotional meetings
- the sponsorship of scientific 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 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).