PRESCRIPTION MEDICINES
CODE OF PRACTICE AUTHORITY

# CODE OF PRACTICE REVIEW

NUMBER 15

FEBRUARY 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.

## More inter-company complaints..... but less complaints from health professionals

**The Authority received 102 complaints in 1996, slightly less than the 104 received in 1995. These figures compare with the 145 received in 1994. In the years immediately prior to 1994, the number of complaints received each year was in the approximate range of 80-100 a year and in no year prior to 1994 had the number of complaints exceeded 100. Experience in 1995 and 1996 suggests that the number of complaints has reverted to the long term pattern and that the high number of complaints in 1994 will prove to be an anomaly.**

**The year did, however, show a notable change in the sources of complaints. In previous years the majority of complaints came from health professionals. In 1995, for example, 64 complaints were from health professionals with only 26 coming from companies. In 1996, however, only 40 came from health professionals while 47 were received from companies. This exceeds the previous high of 41 inter-company complaints in 1994.**

**Some information about the number and sources of complaints received in 1996 was given in the November issue of the Code of Practice Review. In response to that "Scrip" (14 January 1997) speculated, under a heading "Unaffordable ethics in the UK?", that it was one of the effects of tougher market conditions.**

**The ABPI encourages its members to try to settle differences between them by negotiation before submitting complaints to the Authority and the majority of inter-company complaints show that this has been attempted. Inter-company complaints do have an important role to play in a self-regulatory system as competitor companies are often the best placed to see problems in other companies' materials.**

### Your sins were nearly washed away!

The Authority's records, and indeed Code of Practice records dating back to before the establishment of the Authority in 1993, are kept in a large walk-in safe at 12 Whitehall, a relic of the days when it was part of the adjacent bank which still owns the premises. Despite the use of this facility, the records were saturated with water when a leak occurred during the renovation of the ABPI's premises above. Companies need not, however, fear that the records of their transgressions are forever lost! The case records are being freeze dried and it is anticipated that they will be returned as good as new!

### Substantiation must be by material available to enquirers

Clause 7.3 of the Code states that "Any information, claim or comparison must be capable of substantiation" and Clause 7.4 states that "Substantiation for any information, claim or comparison must be provided without delay at the request of members of the health professions or appropriate administrative staff".

It follows, therefore, that everything in an advertisement must be able to be substantiated by material which the company is prepared to supply to health professional enquirers, even when those enquirers are employed by competitor companies. In one or two recent cases, companies have attempted to substantiate claims by material which they regarded as confidential and which they were not prepared to provide to health professionals seeking substantiation. Such a reservation cannot be made. Similarly, copyright problems cannot be used as a valid reason for failure to substantiate. Substantiating materials have to be made available in accordance with the Code. If for any reason they cannot be, then the claim in question cannot be made.

### References incorporating other companies' brand names

Clause 7.5 of the Code states that "When promotional material refers to published studies, clear references must be given" and Clause 7.10 states that the "Brand names of other companies' products must not be used unless the prior consent of the proprietors has been obtained." A case reported in this issue of the Review (Case AUTH/463/9/96) evidences a potential conflict between these requirements.

The need to reference according to Clause 7.5 does not override the prohibition on the use of brand names in Clause 7.10. If a reference which uses another company's brand name has to be used, and consent for such use cannot be obtained from its proprietor, then it should be edited out. This can be done by replacing the brand name with the generic name in square brackets. It is hoped, however, that the proprietor of a brand name in this position will give consent to such limited use on the rare occasions when the problem arises.

### Are we picking on you?

Scrutiny of published journal advertisements by the Authority occasionally results in companies contacted about possible breaches of the Code complaining that they are being picked on.

The Authority picks on no company in particular. Under the scrutiny procedure the Authority picks on any company which it considers is publishing a journal advertisement which is in breach of the Code. Lately, for example, the Authority has taken a number of journal advertisements up with the companies concerned because they failed to comply with the requirements of Clauses 4.2 and 5.4 that the generic name placed adjacent to the most prominent display of brand name must be not less than 10 point bold. Companies were forewarned in the August issue of the Review that such advertisements would be taken up.

### Visit of WHO Fellow

In November the Authority was visited by Mr Shaik Nurudin Bin Shaik Shahrudin, the Assistant Director of Pharmaceutical Services in the Ministry of Health in Malaysia, who was on a WHO Fellowship to study the control of advertising.

Mr Shahrudin attended one of the Authority's seminars on the Code of Practice and spent time at its offices learning about the procedures which were in use. During his stay in the United Kingdom Mr Shahrudin also visited the Medicines Control Agency and the Proprietary Association of Great Britain.

## Syndicate Leaders

Volunteers are sought to act on an occasional basis as syndicate leaders at the PMCPA seminars on the Code which are held at the Royal Society of Medicine in London.

There is no financial reward (though appropriate hospitality is provided!) but those taking on the role find it worthwhile and consider that it assists them in widening their knowledge of the Code.

If interested, please contact Jane Landles (0171-747 1415).

## 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 procedure 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:

Thursday, 17 April 1997
Wednesday, 14 May 1997
Wednesday, 25 June 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 Emer Flynn 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 Emer Flynn (0171-930 9677 extn 1443).

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

| | |
|---|---|
| David Massam | 0171-747 1405 |
| Heather Simmonds | 0171-839 1058 |
| 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/433/5/96

# DIRECTOR/MEDIA v SERVIER

## Promotion of Coversyl

**A letter in The Lancet from MaLAM, an Australian organisation, which was critical of the promotion of Coversyl by Servier, was taken up as a complaint in accordance with established procedure. The claim referred to in the letter was "Coversyl is proven to remodel hypertensive arteries". That claim had not been used in the UK but a similar claim, "Proven to reverse cardiovascular remodelling", had been used.**

**The Panel accepted that Servier had evidence to show that Coversyl had an effect on arterial structure but considered that there was little evidence to show that arterial changes were accompanied by clinical benefit. When associated with an antihypertensive treatment the claim would be taken to imply clinical benefit and the Panel considered that this was misleading. Servier accepted this but appealed because it was unwilling to agree not to use the word "proven" even in a non clinical context.**

**The Appeal Board upheld the Panel's ruling. It did not accept that the evidence was sufficient to enable use of the word "proven" as this was an extremely strong claim and required strong evidence.**

### COMPLAINT

A letter from MaLAM (Medical Lobby for Appropriate Marketing) Inc of Australia published in The Lancet, 18 May 1996, questioned the promotion of Coversyl (perindopril) by Servier. In accordance with the established procedure, the matter was taken up as a complaint under the Code with the Director acting as the complainant. Servier Laboratories Ltd, although not a member of the ABPI, had nevertheless agreed to comply with the Code.

The claim queried by MaLAM was "Coversyl is proven to remodel hypertensive arteries". The authors of the letter accepted that the hypothesis about reversal of vascular changes induced by hypertension had a place in research. They did not agree that the hypothesis was proven. Further, there was no evidence to correlate "remodelling" with any clinically important morbidity or mortality advantage. Consequently the use of the hypothesis in the promotion to general practitioners of one antihypertensive over others was misleading. Servier cited two small studies of gluteal biopsy. The authors of the Thybo study said that the discrepancies between the study and a previous study (by Schiffrin) emphasised that "caution must be taken in the interpretation of results from small studies like ours (25 patients) and that of Schiffrin *et al* (17 patients)". In a study by Sihm, 14 out of the 23 patients received another antihypertensive in addition to perindopril. Servier had cited other studies that assessed vascular compliance and distensibility only. The authors of one study (Kool *et al*) concluded "After discontinuation of either therapy, all effects were rapidly reversed, which suggests rapid reversal of functional changes and does not provide evidence for structural changes in the arterial wall, although small structural changes cannot be excluded".

MaLAM had complained to the Australian Pharmaceutical Manufacturers Association (APMA) but three months later Servier, which was not a member of APMA, had not yet agreed to have the complaint heard by the APMA.

In writing to Servier, the Authority said that the first matter to address was whether the claim "Coversyl is proven to remodel hypertensive arteries" or a similar claim had appeared in material used in the United Kingdom. If it had then it would be necessary for the company to address the criticisms made in the MaLAM letter. If no such claim had been made in the UK, then the ABPI Code of Practice would not apply.

### RESPONSE

Servier said that it was not a member of the APMA but had offered to submit its case to the APMA provided that MaLAM gave an assurance that it would regard the APMA judgement as the final word on this issue. The APMA had not received a reply from MaLAM.

The company submitted that at no time had the claim "Coversyl is proven to remodel hypertensive arteries" been used in the UK. The company provided a copy of a recent Coversyl advertisement which appeared in MIMS June 1996 and included the claim "Proven to reverse cardiovascular remodelling".

Servier submitted that cardiovascular remodelling was an established and generally scientifically well accepted concept. Current opinion would put forward the premise that the cardiovascular remodelling that occurred both in the heart and arteries during hypertension contributed significantly to the mortality and morbidity associated with the disease. As a result, antihypertensive therapy should ideally be aiming to not only lower blood pressure but also to reverse or at least halt the deletrious remodelling process. The company provided a number of papers to highlight and explain further this concept.

Servier submitted that the role of ACE inhibitors in reversing cardiovascular remodelling was now well accepted. Many other ACE inhibitors apart from Coversyl had been studied in this respect and the positive effects of ACE inhibition were probably a class effect. A paper by Opie stated that the concept of changes in vascular structure occurring in hypertension was not new and that experimental and clinical evidence with the use of ACE inhibitors showed that arterial and arteriolar changes associated with hypertension could at least in part be reverted towards normal. Further, while these effects on vascular structure were likely to be a class effect of ACE inhibitors, it was perindopril that seemed best tested for the vascular effects followed by captopril. Servier also pointed out that promotional material for another ACE inhibitor made claims related to this theme.

Servier submitted that Coversyl was the acknowledged leader in this field and the company had actively pursued a wide range of research to further confirm Coversyl's

effect on cardiovascular remodelling and to seek to define an explanation for this positive benefit over and above simple blood pressure reduction. The company had also looked to broaden the scope of the research by looking at Coversyl's other cardioprotective effects. A number of studies to support this view were provided. As a result of this evidence Servier was currently using a claim relating to cardiovascular remodelling in its advertising.

Servier submitted that cardiovascular remodelling was an important part of the hypertensive disease process and this warranted the attention of doctors.

## PANEL RULING

The Panel considered that the claim used in the UK, "Proven to reverse cardiovascular remodelling" was sufficiently close to the claim quoted in the MaLAM letter, "Coversyl is proven to remodel hypertensive arteries", for the matter to come within the scope of that letter. The criticisms in the MaLAM letter applied to the UK promotion of Coversyl.

The Panel accepted that Servier had evidence that perindopril had an effect on arterial structure and that in hypertensive patients the changes that were seen tended to reverse those associated with the disease which were believed to play a part in its complications. The Panel considered that there was little evidence to show that these arterial effects were accompanied by any clinical benefit. Several authors followed the line that the significance of the findings remained to be investigated. The claim was supported in part by the evidence but there were still some doubts about the experimental techniques and whether the vessels studied were representative of all the vascular tree. When associated with an antihypertensive treatment, the claim "Proven to reverse cardiovascular remodelling" would be taken to imply clinical benefit and this had not been proven. The Panel therefore considered that the claim was misleading and ruled a breach of Clause 7.2 of the Code.

* * *

Subsequently there had been discussions between Servier and the Authority over the terms of the undertaking and assurance which would be required in this case but it had not proved possible to reach agreement.

## APPEAL BY SERVIER

Servier said that it was accepted that cardiovascular remodelling predisposed patients with hypertension to serious morbidity and mortality. While studies had shown that ACE inhibitors as a class, and Coversyl specifically, could reverse cardiovascular remodelling, Servier accepted that there was as yet no clear evidence that reversal of cardiovascular remodelling reduced morbidity or mortality.

Servier also accepted that the use of the statement "Proven to reverse cardiovascular remodelling" as a headline in an advertisement could be taken to imply clinical benefit and accepted that, in the absence of sufficient evidence to support clinical benefit of cardiovascular remodelling, this was therefore misleading and in breach of Clause 7.2.

Servier remained convinced that the statement itself "Proven to reverse cardiovascular remodelling" was accurate and justified by the body of research data. Servier was therefore not able to accept the undertaking which required that this statement would no longer be used, although it was prepared to undertake that it would no longer be used in a way or context which implied clinical benefit. Servier was also unable to undertake that any similar statement would not use the word "proven".

Sustained hypertension was associated with changes in vascular structure. Hypertensive vessels in animals and humans were characterised by a thickened media, a reduced lumen and an increased extracellular matrix. This "remodelling" was an active process of structural alteration and appeared to occur in large and small arteries throughout all tissues. These alterations in vascular structure and function predisposed patients with hypertension to the sequelae of this disorder - atherosclerosis, myocardial ischaemia, stroke and renal failure.

The role of the vasculature in hypertension could be summarised as follows:

- hypertension was associated with an increased mean arterial pressure and increased peripheral resistance due to decrease in calibre of small (resistance) arteries or arterioles
- in addition there was a pulsatile component to blood pressure which was also often altered in hypertension and the determinants of this pulsatile component (systolic blood pressure, diastolic blood pressure, pulse wave velocity and reflected waves) depended on the quality of the large (conduit) arteries.

The importance of taking the vasculature into account and not just blood pressure levels when treating an hypertensive patient became apparent when considering the results of intervention trials in hypertension. Blood pressure lowering therapy failed to decrease coronary morbidity to a satisfactory extent (around 20% reduction) as opposed to its efficacy on stroke incidence reduction (around 40% reduction). A likely explanation was that function and structure of the vasculature, here the coronary arteries, was not normalised at the same time as blood pressure and could have been responsible for persistent morbidity.

Antihypertensive treatment could very successfully reduce blood pressure, but it was much less successful in reducing mortality and morbidity from these disorders. This highlighted the possible importance of influencing the remodelling process.

Numerous studies had attempted to define the influence of a variety of antihypertensive agents on vascular remodelling. The most consistent effects had been observed with ACE inhibitors, which had been shown to reverse at least in part the arterial and arteriolar changes associated with hypertension. This appeared to be a class effect.

Coversyl was however an acknowledged leader in this field: "while these effects on vascular structure are likely to be a class effect of ACE inhibitors, it is perindopril that seems best tested for the vascular effects, followed by captopril" (Harrap SB *et al*). Servier had actively pursued a wide range of research, experimental and clinical, to confirm Coversyl's effect on cardiovascular remodelling.

Media to lumen was an important physiological criteria when assessing vascular structure of resistance vessels. Even when diameters were equal, *in vivo* the vasomotor response to any change in flow or pressure would not be the same but would depend on the media thickness.

### Effects in small arteries

**Animal data** - When animals with genetic hypertension, spontaneously hypertensive rats, were treated from weeks four to 16 of age with perindopril, blood pressure failed to rise again to the untreated level after cessation of therapy. This study was among the first to suggest that a fundamental abnormality in these hypertensive animals had been corrected by the use of this ACE inhibitor, over and above mere blood pressure reduction during treatment.

To address this issue further, two ACE inhibitors and three other antihypertensive drug classes, given at equipotent doses, were compared (Chritensen KL *et al*). Spontaneously hypertensive rats were treated from weeks four to 24 with perindopril, captopril, hydralazine, isradipine or metoprolol, administered in the drinking water. The media-lumen ratios of mesenteric vessels were compared: it was completed normalised in the perindopril-treated group, was not influenced by metoprolol, and was only partially affected by captopril, isradipine and hydralazine. The decrease in media-lumen with perindopril was achieved not only by a significant increase in the lumen diameter but also by a significant decrease in the thickness of the media. Hence the two ACE inhibitors, although given at equipotent doses (perindopril 3 mg/kg daily, captopril 60 mg/kg) did not produce the same structural effect. The blood pressure control with captopril was less satisfactory than in the perindopril group.

After discontinuation of therapy, blood pressure returned to untreated levels in the non ACE inhibitor treated animals, while in the ACE inhibitor groups the rise in pressure observed was characteristically slow and did not reach untreated levels.

The relevance of the mesenteric artery as a surrogate for the other vascular beds was illustrated by a study assessing simultaneously the mesenteric, femoral, cerebral and coronary beds (Thybo NK *et al*). After 20 weeks of perindopril treatment, in all four vascular beds a significant, dose-dependent, increase in lumen diameter, a decrease in media thickness and a decrease in media-lumen ratio was observed.

**Human data** - The effects of perindopril on resistance vessel structure were also tested in humans, using the same parameter of physiological significance, media-lumen ratio. In a nine-month open study, 25 hypertensive patients received a perindopril based treatment. To achieve target blood pressure, dosage was first doubled, then isradipine or hydralazine were added if necessary. Before and after nine months of treatment, gluteal biopsies were taken under local anaesthetic from which two small arteries were dissected and mounted on a myograph for morphometry. These small arteries were taken as representative of the resistance vessels of the vasculature (based on Thybo). Media-lumen ratio was normalised: it decreased significantly from baseline, and achieved a level not significantly different from controls. Interestingly, this vascular normalisation was associated with a normalisation of left ventricular mass.

When the sub-group of patients exclusively on perindopril was examined, the same held true: media-lumen was significantly reduced under perindopril.

This study was the first to show that it was possible with an antihypertensive drug to normalise media-lumen ratio of resistance vessels in humans, and that the effect could be obtained within nine months.

The next step was to perform such a study in a comparative way (Thybo NK *et al*). Twenty-five previously untreated hypertensive patients were randomly assigned, in a double-blind manner, to either an ACE inhibitor, perindopril (n=13), or a beta blocker, atenolol (n=12), for one year. Perindopril caused a significant reduction in the media-lumen ratio whereas atenolol had no effect on media-lumen ratio, although there was no difference in blood pressure at one year between the two treatment groups.

The conclusion was that in previously untreated hypertensive patients, perindopril and atenolol affect the structure of the small arteries differently. Perindopril was able to normalise media-to-lumen ratio independently of its effect on blood pressure decrease.

### Effects in large arteries

The quality/structure of the large arteries was a major determinant of the pulsatile component of blood pressure: systolic blood pressure, diastolic blood pressure, pulse pressure.

**Animal data** - Stiffness of the common carotid artery and systemic compliance was studied in three animal groups: normotensive rats, hypertensive rats treated with perindopril and untreated hypertensive rats. Systemic and carotid arterial compliance were significantly increased in the treated animals compared to controls. These improvements of functional properties were associated with significant improvements in the structure of the aortic wall (reduction in media thickness, smooth muscle cell hypertrophy, reduction in collagen content).

**Human data** - Large arteries could not be studied directly in humans but required non invasive and simultaneous assessment of volume and intra-arterial pressure at a given arterial site. The available techniques were recent and combined echodoppler and echotracking.

Perindopril was assessed in a chronic study where 16 hypertensive patients were treated with perindopril over a period of 12 months, interrupted by a one month placebo period from month three to four. During both active treatment periods a progressive increase of brachial artery diameter and brachial artery compliance was observed.

The next step was to assess vascular compliance in a comparative way. In a six month double blind parallel group study, hypertensive patients received either perindopril 4mg or moduretic (hydrochlorothiazide 25mg + amiloride 2.5mg), both drugs being doubled if necessary to achieve blood pressure control. These six months of active treatment were followed by a three month placebo period after which patients were reassessed.

Although a significant and similar decrease in blood pressure was observed in both groups after six months, the vascular effects differed: compliance and distensibility of the brachial, femoral and carotid artery were significantly improved by perindopril whereas only the brachial artery compliance and distensibility was improved by moduretic.

Taken together these studies suggested that perindopril had effects on the diameter and the function of the large arteries independent of blood pressure changes. These effects might be due to direct relaxation of arterial smooth muscle but also to endothelium-mediated actions.

### Effect on left ventricular hypertrophy

As in vascular remodelling, ACE inhibitors had been shown to be more effective in reversing left ventricular hypertrophy than other drug classes, for a similar efficacy on blood pressure decrease.

In a study by Sihm, left ventricular mass reduction was assessed after nine months perindopril therapy in 25 hypertensive patients. Twenty age and sex matched normotensives were used as controls. During antihypertensive treatment, mean BP was reduced from 128+11 to 103+6 mmHg. Left ventricular mass and left ventricular mass index were normalised, ie not different from control values. This reversal of LVmass was due to significant decreases in septum and posterior walls.

In a comparative study, 24 end-stage renal failure patients were treated for one year in a double-blind randomised way with either perindopril or nitrendipine, a calcium channel blocker, for one year. Both treatments induced significant and similar decreases in blood pressure. A decrease in left ventricular mass was observed only in patients receiving perindopril whereas nitrendipine had no effect. "In ESRD (end-stage renal dysfunction) patients, ACE inhibition with perindopril decreases left ventricular mass independently of its antihypertensive effect".

* * *

It was now accepted that cardiovascular remodelling in hypertension predisposed patients to serious sequelae. Reversal of remodelling might therefore reduce morbidity or mortality, although, as yet, there was no evidence to confirm this.

There was evidence that ACE inhibitors as a class reversed remodelling and studies in animal and man indicated that treatment with perindopril was associated with reversal of the functional and structural changes due to hypertension in small and large arteries and in the left ventricle. Continuing research and discussion was clearly important to determine the clinical significance of this.

Servier considered that the statement "Proven to reverse cardiovascular remodelling" was accurate and substantiated by data. Servier further considered that its use in promotional material in a context which did not imply clinical benefit would not be misleading and would not therefore constitute a breach of the Code.

The company drew attention to the fact that the summary of product characteristics (SPC) for Coversyl had been amended in October 1996 and now included the statement "In man, perindopril has been confirmed to demonstrate vasodilatory properties, to restore elastic properties of the arterial blood vessels and to decrease left ventricular hypertrophy". Servier appreciated that this change postdated the use of the claim in question. The evidence available for the change in the SPC was, however, the same as that now before the Appeal Board.

At the appeal the company acknowledged that some of the studies had small patient numbers and that some of the patients were taking additional therapy to perindopril such as a diuretic. The company also acknowledged that there were other studies, some of which were neutral or equivocal with regard to cardiovascular remodelling. This might be due to the model used and the fact that it took time to develop the techniques which were more reliable today.

## APPEAL BOARD RULING

The Appeal Board noted that Servier accepted that the use of the statement "Proven to reverse cardiovascular remodelling" as a headline in an advertisement could be taken to imply clinical benefit and that Servier accepted that, in the absence of sufficient evidence to support clinical benefits of cardiovascular remodelling, this was therefore misleading in breach of Clause 7.2.

The Appeal Board shared the view of the Panel that Servier had evidence that perindopril had an effect on cardiovascular structure and that in hypertensive patients the changes that were seen tended to reverse those associated with the disease which were believed to play a part in its complications. The Appeal Board also shared the view of the Panel that there was little evidence to show that these arterial effects were accompanied by any clinical benefit, a point which had been accepted by Servier.

The Appeal Board did not accept that the evidence was sufficient to enable Servier to use the word "proven". It was an extremely strong claim and required strong evidence. The Appeal Board considered that the scientific interpretation of "proven" would be "beyond reasonable doubt". The data were considered to be insufficient to support such a claim.

The Appeal Board upheld the Panel's ruling that there had been a breach of Clause 7.2 of the Code and considered that the undertaking to be given by Servier in response to this would have to include an undertaking not to use the word "proven", as had been requested by the Authority.

The appeal therefore failed.

**Proceedings commenced** **22 May 1996**

**Case completed** **2 December 1996**

CASES AUTH/446/7/96, AUTH/449/7/96, AUTH/467/10/96 & AUTH/470/10/96

# ZENECA PHARMA, HOSPITAL DOCTOR, HOSPITAL DOCTOR & DIRECTOR/MEDIA v ORION PHARMA

## Promotion of Fareston

**Three complaints (from Zeneca & two hospital doctors) were received about the promotion of Fareston by Orion Pharma. A letter published in the British Medical Journal critcising the promotion of Fareston was taken up as a further complaint in accordance with established procedure.**

**The Panel ruled that the material at issue, three journal advertisements and a brochure, was misleading and unbalanced in breach of the Code. There was insufficient evidence to support the impression given that tamoxifen was linked clinically with cancer and Fareston was not. Too much was made of the limited animal data given that its relevance to the clinical situation was not certain. These rulings applied in all four cases and were upheld by the Appeal Board on appeal by Orion Pharma.**

**Zeneca alleged that one advertisement was a teaser advertisement. The Panel decided that the advertisement gave too much information for it to be a teaser. Readers would know that the product was for breast cancer. A breach of the Code was ruled as no prescribing information had been provided.**

**The Panel accepted an allegation from Zeneca that the impression of an advertisement was that the indication for Fareston was unrestricted and similar to that of tamoxifen. This was not so. Fareston was licensed for first line hormone treatment of hormone dependent metastatic breast cancer in post menopausal patients and tamoxifen was licensed for the treatment of breast cancer. The Panel ruled that the advertisement promoted Fareston outside its product licence and was misleading.**

Zeneca Pharma and two hospital doctors complained about the promotion of Fareston (toremifene) by Orion Pharma (UK) Ltd. A letter published in the British Medical Journal, 12 October 1996 criticised the promotion of Fareston and was taken up as a complaint under the Code in accordance with established procedure.

The material at issue was three journal advertisements and a brochure.

Orion Pharma although not a member of the ABPI, had nevertheless agreed to comply with the Code.

### CASE AUTH/446/7/96

There were three allegations which were considered as follows:

### 1 Teaser advertisement

The advertisement at issue (ref FAR0006) appeared in the British Medical Journal (BMJ), 8 June 1996. It carried the copy "Baths Bleach Breast Cancer The chlorine connection." This was followed by the company name followed by the statement "Our attention to detail makes an oncological difference". At the bottom of the advertisement there was a statement that further information was available on request and the company name and address was given.

Attention was also drawn to a closely related launch advertisement (ref FAR0007) for the product, Fareston, which appeared in The Pharmaceutical Journal at the beginning of July. This advertisement contained the same opening claims "Baths Bleach Breast Cancer The chlorine connection" followed by details about Fareston and the prescribing information.

### COMPLAINT

Zeneca alleged that the teaser advertisement was in breach of Clause 9.1 of the Code. It gave an indication, breast cancer, and mentioned an attribute, the chlorine atom. Toremifene was a chlorinated derivative of tamoxifen, a point which became clear in the subsequent launch advertisement. Orion Pharma, as far as Zeneca knew, did not have any products available in the UK other than Fareston and the BMJ advertisement was clearly product related and not purely corporate.

### RESPONSE

Orion said that Zeneca had written to it directly and its response was that the BMJ advertisement was a corporate advertisement and not a teaser. The corporate campaign finished at the end of June and therefore Zeneca's request for action was met indirectly and the issue resolved.

Subsequently, Orion received a letter from the Authority as a result of the routine scrutiny procedure, questioning the advertisement with respect to Clauses 3.1, 4.1 and 9.1 of the Code. Given the Authority's comments on the advertisement, the company accepted that it went beyond a corporate advertisement. Orion had advised the Authority that at the time the advertisement was used, the company had got a marketing authorization for Fareston.

Orion said that it did have a licence for a second oncology product and a range of chemotherapy products currently planned to be introduced at the beginning of 1997. The corporate advertisement was released against this background.

### PANEL RULING

The Panel considered that the BMJ advertisement was not a teaser advertisement as defined in the supplementary information to Clause 9.1 of the Code. Teaser advertisements were defined as material which elicited an interest in something that would be following or would be available at a later date without providing any actual information about it. The advertisement in question gave too much information for it to be a teaser. Readers would know that Orion had a product for breast cancer with chlorine having some relevance to the product. No breach of Clause 9.1 was ruled. The Panel considered that the advertisement was an advertisement for Fareston and prescribing information should have been included. A breach of Clause 4.1 was therefore ruled.

## 2 Promotion outside the marketing authorization

The advertisement in question (ref FAR0011) was headed "Breast cancer is worry enough" and appeared in Pulse, 6 July 1996, as well as in a number of other publications.

### COMPLAINT

Zeneca pointed out that the indication for Fareston was "First line hormone treatment of hormone dependent metastatic breast cancer in postmenopausal patients". The much wider indication for its own product, tamoxifen, was "The treatment of breast cancer". This encompassed early and metastatic breast cancer in both pre and postmenopausal women. The advertisement did not mention the restricted indication for Fareston. Zeneca acknowledged that it was mentioned in the small print in the prescribing information but many readers would not notice this and would assume that the indication was that outlined in the copy.

The advertisement implied that the indication for Fareston was wider by the use of the headline "Breast cancer is worry enough" and the strap line "Now you have a choice in anti-oestrogen therapy". There was only a choice for a proportion of breast cancer patients if Fareston was used for its licensed indication. The overall impression of the advertisement was that the indication for Fareston was unrestricted and similar to that of tamoxifen.

Zeneca alleged that the advertisement was in breach of Clause 3.2 of the Code. Further it was ambiguous and misleading with regard to the licensed indication in breach of Clause 7.2.

### RESPONSE

Orion reproduced the exact words of its indication in abbreviated advertisements but submitted that this role was fulfilled by the prescribing information in full advertisements. This appeared to be consistent with the interpretation of other companies which took the same approach and examples were provided.

### PANEL RULING

The Panel noted that the advertisement at issue was headed "Breast cancer is worry enough". The advertisement referred to tamoxifen and stated "Now you have a choice in anti-oestrogen therapy". The Panel considered that the overall impression of the advertisement was that there was now a choice in the treatment of breast cancer with anti-oestrogens. This was not true because the indication for Fareston given in the summary of product characteristics (SPC) was for "First line hormone treatment of hormone dependent metastatic breast cancer in post-menopausal patients" whereas the indication for tamoxifen given in the data sheet for Nolvadex in the ABPI Data Sheet Compendium 1995-96 was "The treatment of breast cancer", which was much wider. There was only a choice for patients within the indication for Fareston and not all patients with breast cancer. The Panel noted that the indication was given in the prescribing information in the advertisement. The first impression of the advertisement was that the product could be used to treat all breast cancers and this was not so. The Panel considered that the advertisement promoted Fareston outside its marketing authorization and therefore ruled a breach of Clause 3.2 of the Code. The Panel also ruled a breach of Clause 7.2 as the advertisement was misleading.

## 3 The use of animal data

This allegation concerned both the launch advertisement (ref FAR0007) which appeared in The Pharmaceutical Journal in July (referred to in point 1 above) and the advertisement in Pulse 6 July 1996 (ref FAR0011) (referred to in point 2 above).

### COMPLAINT

Zeneca pointed out that a central claim in the advertising copy was based on the small difference in the chemical structure of Fareston (chlor-tamoxifen), compared with tamoxifen whereby the use of tamoxifen led to the formation of epoxide metabolites and Fareston did not. These metabolites were implicated in the formation of DNA adducts and liver carcinoma in rats. From these animal data it was suggested that Fareston would have an advantage over tamoxifen in clinical practice because carcinoma might result from the use of tamoxifen but not Fareston. This fundamental message of the advertising was encapsulated by the following claims in the launch advertisement "So, Fareston may deliver what tamoxifen delivers - and a little bit less", "It's a small change, but it makes a big difference" and "Our attention to detail makes an oncological difference".

Zeneca alleged that the implied clinical advantage for Fareston was reinforced by the following claims in the advertisement in Pulse. "Breast cancer is worry enough", "There are doubts about tamoxifen" and ".. all women on tamoxifen therapy should be monitored for carcinogenic effects". This advertisement was scare raising by the use of the above claims and the use of a picture of an extremely worried woman. The reference to animal data in this advertisement was not directly linked to the reference to "... doubts about tamoxifen" however, it was mentioned in the adjacent paragraph thereby leaving a unclear impression as to the basis upon which it was said that these doubts arise. The description of Fareston as "second generation" also implied a clinical advantage for Fareston.

Zeneca noted that the launch advertisement (ref FAR0007) did acknowledge that caution was needed in extrapolating animal data. The advertisement acknowledged that it was uncertain whether the inference referred to was justified by the use of the statement "Although a direct inference cannot be made with certainty, ...". Zeneca alleged that this admission simply reinforced the fact that the central claims were misleading.

Zeneca pointed out that there was no clinical evidence to suggest a possible difference in the incidence of liver carcinoma between tamoxifen and chlor-tamoxifen, but the whole Orion campaign was based on the implications of such a distinction. Fareston had been available for only a short time and such data as existed from comparative trials showed no tolerability (or efficacy) advantage for chlor-tamoxifen over tamoxifen (Hayes *et al* 1995 and

Howell *et al* 1996). The prescribing information for Fareston stated under "precautions and warnings" that experience of long term use (more than one year) was limited. In contrast tamoxifen had been widely used for around 25 years and there was 7.5 million patients data available.

The inferences and claims for clinical superiority for Fareston and the emphasis placed on limited animal data were the more unacceptable. Firstly, because the relevance of the tamoxifen animal data referred to by Orion had itself been strongly questioned and remained controversial and, secondly, because, contrary to the impression given, Fareston had also been associated with the formation of DNA adducts in certain models (Davies *et al* 1995). The issue of DNA adducts and their possible significance was highly complex. Nevertheless there was substantial clinically based evidence indicating that an increased incidence of DNA adducts was not reported in breast cancer patients receiving tamoxifen. Recent investigations were provided (Martin *et al* 1995, Carmichael *et al* 1996, Phillips 1996).

Zeneca also pointed out that the two advertisements made reference to a recommendation of the American Health Foundation concerning the monitoring of patients receiving tamoxifen for carcinogenic effects. This was a reference to a US non governmental organisation whose advice reflected neither the UK nor the US prescribing information for tamoxifen, both of which had been updated quite recently. Nor did it reflect the advice from any other regulatory authority worldwide.

Zeneca alleged that the Orion advertisement implied a clinical advantage for chlor-tamoxifen with respect to the potential to produce cancer. The implication was made solely on the basis of animal data which was itself was of questionable interpretation. There was no data to show animal studies had direct relevance and significance in the clinical situation and it was therefore invalid to make such extrapolations. In fact there was clinical evidence to the contrary in that after 25 years of clinical use of tamoxifen there was no real evidence to suggest that it caused liver cancer in humans. Zeneca alleged that the advertising was in breach of Clauses 7.2 and 7.7 of the Code.

## RESPONSE

Orion pointed out that Zeneca referred to chlor-tamoxifen but toremifene was the approved name for Fareston. It appeared to Orion that Zeneca's major concern was that Orion was using animal data to made a clinical benefit claim for Fareston.

Orion said that it had in no advertisement stated that the animal data predicted human response and as such provided clinical benefit. In order to ensure there was no confusion as to what was animal data, it had, within the advertisements, included the animal species within the text, been specific and referred to the site (liver), ensured the same emphasis was placed upon the text referring to animal data eg typesize and style, provided a clear reference for any animal data quoted and not referred to animal and human data in the same sentence.

Orion agreed that the issue of DNA adducts and their possible significance was highly complex. However, as the situation stood currently, the following conclusions could be drawn from *in vivo* and *in vitro* animal work.

a Tamoxifen was a potent hepatocarcinogen in rats and Fareston was not (Hard *et al* 1993).

b The peroxidase/hydrogen peroxide enzyme system was capable of N-demethylating both tamoxifen and toremifene. In the liver, however, the activation of tamoxifen was catalysed by cytochrome P450 and it was probable that in the rat or human liver, peroxidase activation of tamoxifen or toremifene played only a minor role. This was supported by the fact that dosing rats with toremifene resulted in either no or only trace levels of hepatic labelled adducts. It was therefore at the extrahepatic sites that the role of peroxidase might be more relevant to carcinogenic action (Davies *et al* 1995). This would also account for the difference between the two products stated above in point a.

c The Carmichael *et al* 1996 study referred to by Zeneca recognised that women treated with tamoxifen had an increased risk of developing endometrial cancer with relative risks ranging as high as 7.5. DNA adduct formation was not detected, however, the rationale for this might not be dissimilar to the rat data. The authors stated that "These data suggest that the genotoxic effects observed with tamoxifen in the rat may not apply to the human endometrium" rather than providing conclusive proof against genotoxicity. A recent poster presentation by Pathak *et al* 1996, identified in rats a single DNA adduct in the uterus following seven days treatment with tamoxifen. The poster stated that the DNA adducts formed by uterine peroxidase activation of four-hydroxy TAM (tamoxifen) may play a role in endometrial cancer associated with TAM treatment.

Orion referred to Zeneca's point that there was substantial clinically based evidence indicating that an increased incidence of DNA adducts was not reported in breast cancer patients receiving tamoxifen. In total the number of tamoxifen treated patients investigated in the three studies referred to was 32 (sample studies being 18 endometrial, 7 liver and 7 white blood cells). This was less than substantial and it was important to note the authors' comments from two of the studies. Martin *et al* 1995, stated "We cannot exclude the possibility that a small number of women given tamoxifen may, as a result of a combination of these factors, produce sufficient DNA damage to result in liver cancer nor can we be certain that tamoxifen does not damage DNA in other cell types of other organs". Carmichael *et al* 1996, stated "Chromatography on polyethyleneimine-cellulose TLC plates revealed DNA adducts in endometria treated with alpha hydroxytamoxifen identical to those seen previously in the rat liver." Orion submitted that it was extremely important that any comment on the subject of DNA adduct formation was specific and not generalised. This was why it had taken the approach previously outlined.

Orion then dealt with the advertisements separately. With regard to the launch advertisement (ref FAR0007) Orion submitted that the "big difference" was explained within the copy which made it clear that it related to the formation of DNA adducts and hepatocarcinogenicity in rats. No claim was made for a human difference and in

fact the similarity between the two products was detailed in a separate paragraph to the animal data reference. The statement "Although a direct inference cannot be made with certainty", was factually correct. The sentence then referred to action taken by the American Health Foundation which was not a US governmental organisation but was simply an example of how some people/groups were thinking. The key point in the statement "So, Fareston may deliver what tamoxifen delivers - and a little bit less" was the word "may". The company was not saying that Fareston would deliver as it equally well might not. The statement was therefore balanced. The statement "Our attention to detail makes an oncological difference" was a property pertinent to Orion. The customer would decide whether it was true or not.

With regard to the advertisement in Pulse (ref FAR0011), the company submitted that the advertisement represented the situation when a woman was told she had breast cancer. Many women would be aware of tamoxifen. Much of the literature they saw on the product referred to an increased risk of endometrial cancer in one way or another and magazines and newspapers frequently discussed all aspects of breast cancer. The copy of this advertisement was reflecting the situation that existed and offered an alternative to tamoxifen for, as stated in the prescribing information, "first line hormone treatment of hormone dependent metastatic breast cancer in post menopausal patients". The animal data reference was specific to rats, separated from any human claims, not emphasised by typesize or style and was clearly referenced. With regard to the term "second generation" the company argued that the genotoxic effect of both products demonstrated in the liver of rats clearly separated the products and alone justified its use.

With regard to the subject of liver cancer in humans as a result of tamoxifen treatment the company submitted that it was not suggesting that this was an epidemic. The absence of DNA adducts in the human liver might be due to human variability, not all were susceptible, and/or inadequate sensitivity of the assay method. The expected number of DNA adducts was small, hence any tamoxifen induced adducts might be lost in the background count that existed. As yet there was no way to identify specific tamoxifen or indeed toremifene generated adducts. Extrapolating high dose tamoxifen in a relatively small number of rats to low dose tamoxifen in a large number of humans suggested that it might be difficult to detect a low incidence of hepatocarcinogenicity. Such detection was further impeded by the fact that post mortems on patients that had died of breast cancer were rarely performed and where other organs, for example the liver, had become involved it was generally assumed their involvement was related to metastases from the original breast tumour. To the company's knowledge there were no sufficiently large or detailed studies on the subject. This absence of evidence was not the same as there being no evidence of effect as suggested by Zeneca.

Orion's claim was that Fareston was not hepatocarcinogenic in rats (Hard *et al*). The rat data that supported the statement was not questionable and the Fareston SPC included reference to this in section 5.3 Pre-clinical safety data. This was in contrast to the latest data sheet for the Zeneca brand of tamoxifen (ABPI Data Sheet Compendium 1995-96) which stated "Tamoxifen was genotoxic in some *in vitro* tests and *in vivo* genotoxic tests in rodents".

### PANEL RULING

The Panel noted that Fareston was a new product and there would be limited data about it. The SPC stated under the section "Special warnings and special precautions for use" that, "Experience of long-term use (more than one year) of toremifene is limited". This was also stated in the prescribing information in both advertisements. Conversely, tamoxifen was a well established product with vast documented clinical experience.

With regard to the use of animal data, the Panel noted it had been made clear in the advertisement that DNA adducts and the hepatocarcinogenicty related to work on rats. In the Panel's view, however, too much was made of the limited animal data given that the relevance to the clinical situation was not certain.

The advertisements would raise concerns with readers that patients on tamoxifen might develop cancers associated with their treatment. In the Panel's view there was not sufficient evidence to support the impression given by the advertisements that tamoxifen was linked clinically with hepatic cancer and that Fareston was not.

Overall, the Panel considered that the advertisements were misleading and unbalanced. There was insufficient evidence to support the distinctions made between the products in the advertisements. Breaches of Clauses 7.2 and 7.7 of the Code were ruled.

## CASE AUTH/449/7/96

### COMPLAINT

A hospital doctor complained about a journal advertisement for Fareston (ref FAR0011). The complainant stated that this was one example of the extensive campaign organised by Orion to subvert the market for tamoxifen in favour of toremifene, an analogue of the parent compound. The complainant said that the advertisement was a disgusting perversion of the truth. There were five or six million women years experience with tamoxifen and the complainant had been personally responsible for randomised control led trials of the drug as adjuvant treatment for early breast cancer involving thousands of women followed up for more than 15 years. The complainant considered that there was a very accurate idea of its side effects. The complainant was well aware of the theoretical concern about carcinogenicity and yet none of the evidence on clinical use of the product had demonstrated an increase in liver cancer in women and even the excess incidence of endometrial cancer after long term usage was quite trivial and perhaps not even real but due to statistical artefacts of observational methodology. There was nothing like that experience with toremifene and the company was therefore not in a position to say that its product was a safer anti-oestrogen.

The complainant believed that the campaign should be stopped partly because it was intellectually dishonest and partly because it might indirectly cause inappropriate

anxiety to women with breast cancer who were already on tamoxifen therapy. Tamoxifen therapy had lead to a 25% reduction in breast cancer morality which had become apparent in the national statistics between 1985 and 1993.

## RESPONSE

Orion accepted that tamoxifen had been the cornerstone of anti-oestrogen therapy for more than 20 years. The benefits in the management of breast cancer were well recognised. The benefit to risk ratio in the treatment of breast cancer was clearly positive.

However concerns regarding the carcinogenic potential of tamoxifen, in particular the increased incidence of endometrial cancer, were prevalent in both the clinician and patient population. Lay press coverage during July 1996 centred on a new leaflet published by the cancer charity Tenovus entitled "Tamoxifen - the facts". The leaflet covered the 20 most frequently asked questions about tamoxifen including "Does tamoxifen cause liver cancer?" and "Does tamoxifen cause cancer of the womb (uterine cancer)?" Clearly concern did exist among patients and the advertisements reflected the concern accurately.

No statement was made regarding the relative safety of toremifene versus tamoxifen in the advertisement. The claim that toremifene was not hepatocarcinogenic in rats was clearly substantiated by the data (Hard *et al* 1993). The Fareston SPC included reference to this fact in section 5.3 whereas the Zeneca brand of tamoxifen stated in its data sheet that "Tamoxifen was genotoxic in some *in vitro* tests and *in vivo* genotoxicity tests in rodents".

In terms of human comparative side effect data, a study by Hayes *et al* involving 648 patients, 215 on tamoxifen and 221 on toremifene on 60mg a day (the standard licensed dose) and 212 on toremifene 200mg per day, concluded that "The activity, toxicity and side effects of (toremifene) in postmenopausal women with hormone receptor positive or unknown metastatic breast cancer are similar if not equivalent to those of (tamoxifen)".

The Calman Report (a policy framework for commissioning cancer services - April 1995) submitted to the Chief Medical Officers of England and Wales recommended that "Patients, families and carers should be given clear information and assistance in a form they can understand about treatment options and outcomes available to them at all stages of treatment from diagnoses onwards". The central theme of the Orion promotion was that a choice now existed for first line hormone treatment of hormone dependent metastatic breast cancer in postmenopausal patients.

With regard to the theoretical concern about carcinogencity with tamoxifen not being reflected in clinical practice, the company said that the following represented a view of the current situation.

a Tamoxifen was a potent hepatocarcinogen in rats. Fareston was not hepatocarcinogenic in rats (Hard *et al* 1993).

b The conclusion of Patnak *et al* that "... DNA adducts formed by uterine peroxidase activation of 4-hydroxy-TAM might play a role in endometrial cancer associated with TAM treatment.

c There was substantial evidence that tamoxifen was carcinogenic in the human endometrium with relative risks ranging as high as 7.5. Papers were submitted to support this view (Fisher *et al*, 1994, Van Leeuwen *et al*, 1994 and King, 1995).

d It was aware of a discussion in the literature regarding the potential for liver cancer although this had not been proven. Extrapolating high dose tamoxifen in a relatively small number of rats to low dose tamoxifen in a large number of humans suggested that it might be very difficult to detect a low incidence of hepatocarcinogenicity, such detection was further impeded by the fact that post mortems on patients that have died of breast cancer were rarely performed and where other organs, for example the liver, had become involved it was generally assumed that their involvement was related to metastases from the original breast tumour. To Orion's knowledge there were no sufficiently large or detailed studies on this subject. The absence of evidence was not the same as there being no evidence of effect as suggested by the complainant with respect to the clinical use of the medicine.

The company submitted that against this background of evidence it was hard to argue that the incidence of endometrial cancer was quite trivial and might not be real. The company experience to date with clinicians had certainly found that the vast majority agreed that there was an increased risk of endometrial cancer with tamoxifen. Given the available evidence it was surprising for someone to argue that the risk might not exist.

With regard to the complainant's view that the advertisement might indirectly cause anxiety to women with breast cancer, Orion submitted that this was a surprising comment as it totally ignored the awareness of tamoxifen and its potential to cause endometrial cancer that existed among many women with breast cancer. This was demonstrated by the leaflet with the 20 most frequently asked questions about tamoxifen referred to above. It appeared that the vast majority of clinicians and breast care nurses recognised this awareness and allowed for it in the counselling of patients.

Orion submitted that the concerns surrounding tamoxifen already existed and would probably grow as patients became more involved in their treatment. The concerns were therefore a real issue in the management of breast cancer and must not be ignored. The objective was to offer Fareston in line with the licensed indication as an alternative to tamoxifen and with a rationale as to why it might be appropriate. The advertisement was, of course, directed to physicians and not to patients.

The company had taken great care in the development of the campaign and submitted it represented very closely the situation that existed from a woman's perspective of being told she has breast cancer and the concerns she might have regarding management of the disease. The statements made were capable of substantiation and did not denigrate tamoxifen but reflected current medical opinion.

## PANEL RULING

The Panel considered that this complaint was covered in Case AUTH/446/7/96 above and therefore its ruling of breaches of Clause 7.2 and 7.7 similarly applied.

## CASE AUTH/467/10/96

## COMPLAINT

A hospital consultant in clinical oncology complained about a brochure promoting Fareston, toremifene (FAR0034) issued by Orion.

The brochure was headed "Breast Cancer is Worry Enough" and went on to discuss the differences between Fareston and tamoxifen. The statement "Concern has been raised about the safety profile of tamoxifen" appeared on the front of the brochure.

The complainant objected strongly to the brochure. He had discussed it with many oncology colleagues who shared his views. His view was that this sort of literature easily found its way into the hands of patients. The complainant said that engendering concerns about tamoxifen in the way that the brochure did was an invidious scare-mongering tactic which would increase the level of anxiety for women with breast cancer. The complainant had already contacted the Advertising Standards Authority but had been told that the matter was not within its remit.

## RESPONSE

Orion said that elements of the brochure were part of an advertisement that appeared in the medical press. There were, however, substantial differences in content. The brochure in question was an information piece for members of the medical profession only. At no time had the brochure been directed to patients and would not increase the level of anxiety for women with breast cancer.

The company submitted that the statement "Concern has been raised about the safety profile of tamoxifen" did not sensationalise the issue but represented in a balanced, fair and objective manner the current situation. Concerns had been raised about the safety profile of tamoxifen and these had been debated in the medical and lay press. Information was freely available to the general public from the Internet. Breast cancer was worry enough for any woman and her family. If because of what she had read about tamoxifen, her concerns were heightened, then a choice of product for certain patients might well be of value to a physician. Until July 1996 no such choice existed.

The brochure compared Fareston, in a group of patients for whom it was licensed, with tamoxifen. The claims were consistent with the SPC. The claims reflected the information upon which they were based and were balanced, fair, unambiguous and up to date. The information and claims about side effects reflected available evidence and were substantiated by clinical experience. The material also contained two statements concerning genotoxicity and carcinogenicity in rats as these applied to Fareston and tamoxifen. Orion submitted that the important point was to interpret the statements correctly. It was incorrect to interpret the statements as a safety claim for humans. The correct interpretation was that in animal models accepted by toxicologists as an indicator for cancer forming potential in humans, Fareston, unlike tamoxifen, was not genotoxic and had demonstrated no cancer forming potential. The statements as presented were scientifically correct, consistent with the SPC for Fareston and the data sheet for tamoxifen (as marketed by Zeneca). The company pointed out that it stopped using this material because of the misunderstanding by some physicians regarding one of the advertisements. It did not however consider the material to be in breach of the Code.

## PANEL RULING

The Panel noted that the brochure was designed for distribution to healthcare professionals. It was not aimed at patients. If such material happened to be seen by patients it was not a matter covered by the Code unless a pharmaceutical company had circulated the material directly to patients.

The Panel considered that its comments in previous cases concerning the promotion of Fareston (Cases AUTH/446/7/96 (point 3) and AUTH/449/7/96) also applied to the case now before it. The Panel therefore ruled breaches of Clause 7.2 and 7.7 of the Code.

## CASE AUTH/470/10/96

## COMPLAINT

A letter in the British Medical Journal, 12 October 1996, criticised the promotion of Fareston by Orion. The matter was taken up as a complaint under the Code in accordance with established procedure.

The authors of the letter were concerned by the Fareston advertisement which appeared in the British Medical Journal, 6 July 1996, and in other journals. The advertisement focused on patients' perceived concerns about the toxicity of tamoxifen, specifically its carcinogenic potential, and proposed toremifene as an alternative that could allay those fears. The issue of endometrial cancer and tamoxifen had stimulated much debate. It should however be seen in context. The national surgical adjuvant breast and bowel project, a trial of adjuvant tamoxifen, showed roughly a twofold increase and risk of endometrial cancer but overall benefit far outweighed this risk.

The authors stated that whatever the concerns about tamoxifen, to use them in promoting toremifene was inappropriate. Firstly, toremifene did not have a licence for use as adjuvant treatment, the setting in which the question of endometrial cancer had been raised. Toremifene was licensed for use only in patients with advanced breast cancer. There was no evidence that the occurrence of endometrial cancer affected the outcome for this group of women treated with tamoxifen. Secondly, although there might be experimental grounds for believing that toremifene was less likely to be carcinogenic than tamoxifen, there were no clinical data to support the contention. Not surprisingly in a randomised comparison of tamoxifen and toremifene, no patient developed endometrial cancer. Indeed there was no

difference in either activity or adverse events between the two treatments. Thirdly, the SPC for toremifene specifically described "... a risk of endometrial changes including hyperplasia, polyps and cancer" and toremifene was contraindicated in women with pre-existing endometrial hyperplasia. Finally, the potential risks associated with tamoxifen came with prolonged use, yet the SPC for toremifene warned that experience of use of the product for more than one year was limited. In contrast there had been more than seven million women years of use of tamoxifen.

The authors stated that the advertisement was unbalanced and misleading, used preclinical data unsupported by clinical studies and appeared to contravene the Code. Patients' concerns were important but it was surely unethical to play on these concerns when there were no clinical data showing that the use of toremifene in place of tamoxifen would reduce the incidence of endometrial cancer.

## RESPONSE

Orion said that the authors clearly focused on the Fareston journal advertisement (ref FAR0011) which had been previously ruled to be in breach of Clauses 7.2 and 7.7 of the Code (Cases AUTH/446/7/96 (point 3 above) and AUTH/449/7/96). Orion had appealed against the Panel's ruling in these cases.

Orion had responded in the British Medical Journal to the letter at issue. In addition, the company said it was not certain as to what was meant by "patients' perceived concerns about the toxicology of tamoxifen". In the company's view they were genuine concerns and this was supported by a publication entitled "Tamoxifen - The Facts" issued by the cancer charity, Tenovus. This publication covered the top twenty most commonly asked questions about tamoxifen, which included "Does tamoxifen cause cancer of the womb (uterine cancer)?" and "Does tamoxifen cause liver cancer?".

In its published response Orion made the point that the advertisement made no mention of endometrial cancer. In its response to the Authority, Orion pointed out that the authors of the letter to the British Medical Journal had focused on endometrial cancer as a result of the advertisement. The authors had interpreted the DNA adduct statement, "The evidence is there that Fareston - a 2nd generation analogue of tamoxifen - does not cause DNA adducts and is not hepatocarcinogenic in rats" as being linked to a lower incidence of endometrial cancer with Fareston rather than tamoxifen. The interpretation of the statement regarding animal data was again a key issue. The correct scientific translation of the statement was that Fareston was not genotoxic and had demonstrated no liver cancer forming potential in an animal accepted by toxicologists as an indicator for cancer forming potential in humans. It did not translate to, Fareston would have a lower incidence of liver or endometrial cancer than tamoxifen in humans as the animal models were not a predictor of target site in humans. If a reader chose to misread or misinterpret what was stated it did not mean that it was incorrect or in breach of the Code.

## PANEL RULING

The Panel noted that the advertisement did not refer specifically to endometrial cancer. It did refer to a recommendation that patients on tamoxifen should be monitored for carcinogenic effects and it also stated that Fareston did not cause DNA adducts and was not hepatocarcinogenic in rats.

The Panel considered that its comments in previous cases (AUTH/446/7/96 (point 3), AUTH/449/7/96 and AUTH/467/10/96) also applied to the case now before it. The Panel therefore ruled breaches of Clauses 7.2 and 7.7 of the Code.

## APPEAL BY ORION IN ALL FOUR CASES

Orion submitted that there was a misunderstanding regarding the role of pre-clinical data and its relevance to the prescribing decision when a choice was being made between toremifene or tamoxifen. Pre-clinical toxicology was carried out, in part, to identify the potential for causing cancer in humans using accepted animal models. There was no doubt in the literature regarding the genotoxic nature of tamoxifen. In addition, tamoxifen had been shown to be carcinogenic in humans; clinical experience and clinical studies illustrated a significantly increased risk of endometrial carcinoma. Toremifene had not been identified as a genotoxic agent.

Orion referred to background data. Tamoxifen had been the cornerstone of antioestrogen therapy for more than 20 years. The benefits in the management of breast cancer were well recognised. The benefit to risk ratio in the treatment of breast cancer was clearly positive. There was substantial evidence that tamoxifen was carcinogenic in the human endometrium with relative risks ranging as high as 7.5. The company was aware of discussion in the literature regarding the potential for liver cancer although this had not been proven. To its knowledge there were no sufficiently large or detailed studies on this subject. Tamoxifen was a potent hepatocarcinogen in rats. This was not the case for toremifene. Patients were well aware of the potential risks of tamoxifen. Orion referred to lay press articles to support its view.

Orion submitted that the campaign reflected relevant facts to the prescribing decision. These being; the physician's knowledge and experience, a patient's perspective on breast cancer and concerns surrounding tamoxifen. Fareston was then differentiated on the basis of pre-clinical safety data contained within the SPC in that it did not cause DNA adducts and was not hepatocarcinogenic in rats. Put another way, toremifene was not genotoxic and had demonstrated no liver cancer forming potential in an animal model accepted by toxicologists as an indicator for cancer forming potential in humans. This did not translate to: toremifene did not cause liver cancer in humans and tamoxifen did, because it was known that the target site for human carcinogens was not always the same as in rodents. The relevance to a physician was that should they have concerns regarding the genotoxic potential of tamoxifen, an alternative existed for the first line hormone treatment of hormone dependent metastatic breast cancer in postmenopausal patients.

Orion submitted that the small difference in chemical structure between tamoxifen and toremifene did result in

a significant difference in pre-clinical studies. Tamoxifen had been conclusively shown to be genotoxic whereas toremifene had been shown not to be. The company was at great pains not to make a clinical claim based on this data. No claims had been made in the promotional materials for clinical superiority over tamoxifen.

With regard to Zeneca's questioning of the animal data in terms of it being controversial, Orion submitted that Zeneca's implication that the pre-clinical data was questionable was a surprising approach which did not reflect the balance of evidence or the conclusions of a number of key bodies . Orion referred to the difference between the tamoxifen data sheet and the SPC for toremifene, the Medical Research Council's refusal to endorse chemoprevention studies run by the ICRF and the CRC and the fact the World Health Organisation had recently classified tamoxifen as a Class I carcinogen - essentially it had been demonstrated to cause cancer in humans. Toremifene was classified as Class III - essentially insufficient data to draw a conclusion.

Orion accepted that Fareston had been associated with the formation of DNA adducts in certain models but these were models *in vitro*. The results were not in animals and it was totally misleading to question the animal data for Fareston on the basis of these models. Further data was supplied to support the company's position regarding these models. It demonstrated differences between toremifene and tamoxifen in terms of inducing endometrial cancer in the rat.

Orion advised that the final appearance of the launch advertisement was in August 1996 and the journal advertisement last appeared in the October edition of the British Journal of Cancer.

## APPEAL BOARD RULING

The Appeal Board noted that Fareston was a new product licensed as first line hormone treatment of hormone-dependent metastatic breast cancer in postmenopausal patients. Some of the concerns about tamoxifen raised by Orion related to its use in healthy women at risk of developing cancer.

The Appeal Board examined all the material and agreed with the Panel's view that it implied that a patient receiving tamoxifen was more likely to develop cancer than a patient taking Fareston. The materials were comparing tamoxifen, a well established product with vast documented clinical experience, with a new product, Fareston. The SPC for Fareston stated that experience of long term use (more than one year) of toremifene was limited.

In the Appeal Board's view it had been made clear that the DNA adducts and the hepatocarcinogenicity data related to work on rats but too much had been made of the limited animal data given that the relevance to the clinical situation was not certain. There was not sufficient evidence to support the impression given that tamoxifen was linked clinically with hepatic cancer and Fareston was not.

The Appeal Board considered that the Panel's interpretation of the scientific statements in the material was not unreasonable. The scientific information had not been set in context.

The Appeal Board agreed with the Panel's overall view that the material was misleading and unbalanced. There was insufficient evidence to support the distinctions made between the products in the material. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.7 of the Code in each of the four cases.

The appeal therefore failed.

Following its consideration of the appeal, the Appeal Board requested that its concerns over the alarming nature of the advertising be drawn to Orion's attention.

**Complaints received**

| | |
|---|---|
| **AUTH/446/7/96** | **25 July 1996** |
| **AUTH/449/7/96** | **31 July 1996** |
| **AUTH/467/10/96** | **7 October 1996** |

**Complaint proceedings commenced**

| | |
|---|---|
| **AUTH/470/10/96** | **16 October 1996** |
| **Cases completed** | **26 November 1996** |

CASE AUTH/452/8/96

# CONSULTANT PSYCHIATRIST v WYETH LEDERLE

## Psychiatry in Practice journal

**A consultant psychiatrist alleged that a seemingly independent edition of the journal "Psychiatry in Practice" was in fact sponsored by Wyeth for the promotion of Efexor.**

**The Panel noted that Wyeth's declaration of sponsorship was not obvious to readers of the journal and a breach of the Code was ruled. The Panel also noted that, in addition to three pages of advertising for Efexor, the journal contained a sponsored review on the use of the product in the elderly. The journal thus bore advertising for Efexor on more than three pages in breach of the Code.**

**The Panel considered that the editorial content of the journal was acceptable and ruled no breach of the Code. On appeal from the complainant the Appeal Board ruled a breach of the Code, considering that one article was a promotional piece for Efexor disguised as independent copy.**

A consultant psychiatrist complained about the Summer 1996 edition of the journal "Psychiatry in Practice". The journal in question was twenty eight pages long and included advertisements for Efexor, Wyeth Laboratories' product for treating depressive illness. Page 5 of the journal stated that it was "Sponsored by an educational grant from Wyeth Laboratories". This appeared in small type below the list of contents. In the centre was a bound in insert headed "Sponsored Clinical Review" in small type and this consisted of an article on depression in the elderly. Prescribing information for Efexor was included in this section. The rest of the journal consisted of a number of articles relating to depression as well as others of a more general nature.

### COMPLAINT

The complainant alleged that the publication purported to be an independent journal, but was apparently solely sponsored by Wyeth Pharmaceuticals for the sole promotion of Efexor (venlafaxine).

No less than three of its twenty eight pages had large advertisements for Efexor. A further six sides were devoted to a sponsored review of venlafaxine. There were no advertisements or sponsored reviews for any other product in the journal. Supposedly independent news items (such as "News extra") were devoted solely to venlafaxine. Supposedly unbiased articles suggested the use of venlafaxine. Other antidepressants (the complainant could only find one) were only mentioned in negative terms. No other antidepressant agent besides venlafaxine got a positive report.

The complainant asked if this kind of promotional publication purporting to be an independent journal was actually allowed by the Code and, if so, this was a very grave matter and one that showed the pharmaceutical industry in a very bad light.

### RESPONSE

Wyeth Laboratories explained that the journal in question was sent to a mailing list of GPs and psychiatrists (total circulation 22,000) during July 1996. A further 2000 were issued to its representatives.

The journal was previously sponsored by another company and Wyeth took over sponsorship in 1995 with quarterly published issues. The presentation (ie heading, typeface, colour and logo) of the centre article "Sponsored Clinical Review" clearly identified it as being commissioned and edited by Wyeth. The remainder of the journal was under commissioning and editorial control of the publishers. Advertising space was exclusively for Wyeth products.

Wyeth submitted that it was clearly indicated on page 5 that the journal was sponsored by Wyeth. Every page of the sponsored clinical review was clearly identified as such. The journal did not have the sole purpose of promoting Efexor (venlafaxine). Venlafaxine was only mentioned in one of nine articles and in the "News extra" section and there was an article on antidepressants (page 27) that made no mention of venlafaxine.

With regard to the fact that only Efexor advertisements appeared in the journal, Wyeth submitted that as the journal was clearly sponsored by the company no other advertisements or sponsored reviews would be expected. The two advertisements could quite clearly be identified as such. The "News extra" was a review of a recently published paper on venlafaxine. The article on antidepressants referred positively to the use of newer antidepressants as a class in that they were more likely to be used at therapeutic doses.

With reference to the specific clauses of the Code which the Authority had asked Wyeth to consider, there was no specific complaint that information in the journal contravened Clause 7.2. In any event, Wyeth submitted that it did not. Wyeth also denied a breach of Clause 9.1 of the Code because the format and editorial control of the journal recognised the special nature of medicines and the professional standing of the audience.

With regard to editorial control, Wyeth explained that the contractual relationship between Wyeth and the publishers was such that it was agreed and declared that the editorial policy of the journal was a matter for the journal's Editor and Editorial Board and accordingly Wyeth should have no right to be consulted about the contents of the journal and no editorial approval would be sought from Wyeth prior to publication. Articles which referred to any of Wyeth's products or therapeutic areas

of interest might at the publisher's discretion be submitted to Wyeth for the sole purpose of allowing Wyeth to correct any inaccurate or misleading data or statements contained therein. Any corrections advised to the publisher following these submissions would only be made with the approval of the Editor.

Wyeth denied breaches of Clauses 9.9 and 10.1 of the Code as the fact that the journal was sponsored by Wyeth was clearly indicated in the appropriate place in the journal, together with all other publisher's information. The sponsored clinical review was clearly marked as such on every page of the review.

## PANEL RULING

The Panel first noted that the use of sponsored journals was a difficult area and understood why some health professionals would be concerned about such publications. In the Panel's view an independent publication would be seen by health professionals as being one entirely free from sponsorship by pharmaceutical companies such as, for example, the British Medical Journal. The Panel accepted that such journals would of course sell advertising space to pharmaceutical companies.

The Panel noted that the Authority had not seen "Psychiatry in Practice" when it wrote to Wyeth to advise that a complaint had been received and suggest relevant clauses of the Code for the company to consider.

The Panel examined the journal and considered that the appearance of the publication gave the impression that it was an independent journal. The first two pages of the journal were a double page advertisement for Efexor and page 4 was a "Comment" article written by the Editor. Page 5 listed the contents of the journal followed at the bottom of the page by sixteen lines of small, bold and non-bold print, listing the names of the editorial staff responsible for the production of the journal. In amongst this information, in small bold print, was the statement that the journal was sponsored by Wyeth Laboratories. The Panel considered that most readers would not see this statement, buried as it was in amongst other information. Clause 9.9 of the Code required that all material relating to medicines and their uses which was sponsored by a pharmaceutical company must clearly indicate that it had been sponsored by that company. The Panel did not consider that Wyeth's sponsorship of the journal was made sufficiently clear to those reading it and accordingly ruled a breach of Clause 9.9 of the Code. This was accepted by Wyeth.

The Panel noted that the nature of the agreement between Wyeth and the publishers was such that Wyeth had no direct editorial control over the content of the journal. The journal contained some articles directly related to the treatment of depression but also others of a more general nature. The Panel considered that the editorial content of the journal was reasonable and was not biased. The Panel therefore ruled no breach of Clause 7.2 of the Code.

The Panel noted the requirements of Clause 6.4 of the Code that no issue of a journal may bear advertising for a particular product on more than three pages. In addition the supplementary information to the Clause stated that inserts, whether loose or bound in, counted towards the three pages allowed. The Panel noted that the issue of the journal in question carried one full page advertisement for Efexor on the back cover and one double page advertisement for the product on the inside front cover. In addition the journal contained a sponsored clinical review article on depression in the elderly and the use of Efexor in this patient group. The Panel considered that this article was promotional for Efexor. Prescribing information had been included. In the Panel's view the article was a bound in insert consisting of six pages of advertising. The journal thus bore advertising for Efexor on nine pages. The Panel therefore ruled a breach of Clause 6.4 of the Code. This was accepted by Wyeth.

## APPEAL BY COMPLAINANT

The complainant was concerned about the "News extra" item on page 26 which clearly purported to be part of the independent text. The item again mentioned venlafaxine. Given the whole tenor of the magazine the complainant believed that this news item was promotional material disguised as independent copy and in breach of Clause 10.1.

* * *

When advising Wyeth about the appeal, the Authority pointed out that the complainant referred to Clause 10.1 in the appeal and that the Panel had not made a ruling of no breach of Clause 10.1. The journal, except for the sponsored clinical review section and the advertisements, had not been considered to be promotional material by the Panel and therefore the issue of disguised promotion could not arise. The Panel had ruled that the content was reasonable and unbiased and not in breach of Clause 7.2 of the Code. The implication of the Panel's rulings was that there was no breach of Clause 10.1. The Authority asked Wyeth to comment as regards the appeal in relation to both Clauses 10.1 and 7.2.

## RESPONSE BY WYETH

Wyeth said that with regard to Clause 7.2 it could only refer again to the absence of direct editorial control on its part and endorsed the Panel's view that the editorial content of the journal was reasonable and not biased. The complainant seemed to be arguing that insufficient weight was given by the Panel to the "News extra" item when considering the publication as a whole. This item was simply a review of a recently published paper on venlafaxine and the company failed to see how it supported the complainant's allegation of lack of balance.

Wyeth emphasised that every effort was made to identify clearly the promotional items within the publication. The "News extra" item was not so identified because the company did not consider it to be promotional. Clause 10.1 did not therefore apply.

## FURTHER COMMENTS FROM THE COMPLAINANT

The complainant said that the so - called "News extra" item (which purported to be a report of a recent paper of interest to psychiatrists, and which "coincidentally" happened to be about the journal's sole sponsor's product and which happened to be extremely heavily advertised throughout the entire journal) clearly stated in bold type

that the readers should contact Wyeth medical and gave the telephone number.

The complainant submitted that this clear piece of marketing showed a complete lack of balance. One would not expect to be "led" to the manufacturers of a product by a news item or an independent review of a paper in an independent journal. Being so led to the manufacturer was clearly a promotional device within the text of a so-called independent journal. The complainant submitted that if the whole journal were not so biased it would never have occurred to an independent editorial team to advise their readers to contact a manufacturer.

## APPEAL BOARD RULING

The Appeal Board noted that one aspect of the original complaint was that the journal was a promotional publication purporting to be an independent journal. That was a matter which related to Clause 10.1. The Appeal Board did not consider that the appeal went outside the original allegations but considered that it would have been more helpful if the Panel minute had clearly recorded a decision that there had been no breach of Clause 10.1 of the Code, rather than leaving this to be implied.

The Appeal Board commented that Wyeth's declaration of sponsorship of the journal lacked prominence and was therefore inadequate. The Appeal Board noted that Wyeth had already accepted the Panel's ruling of a breach of Clause 9.9 in relation to this point.

The Appeal Board considered that the "News extra" item had the appearance of independent editorial. The piece was headed "Antidepressant update" but only reviewed a recent study on Wyeth's product, venlafaxine. There was no mention of other studies or other products. The Appeal Board considered that the "News extra" item was a biased insertion into the journal. In view of the fact that readers were invited to contact Wyeth Medical, and given Wyeth's involvement with the journal as a whole, the "News extra" was considered to be a promotional piece for venlafaxine disguised as independent copy. The Appeal Board therefore ruled a breach of Clause 10.1 of the Code.

The appeal in this case was successful.

**Complaint received** **7 August 1996**

**Case completed** **9 December 1996**

CASES AUTH/454/8/96 & AUTH/459/8/96

# NORTON HEALTHCARE & GLAXO WELLCOME v 3M HEALTH CARE

## Letter about Airomir inhaler

**Norton Healthcare and Glaxo Wellcome complained separately about a letter sent out by 3M Health Care which concerned 3M's Airomir inhaler and the Montreal Protocol relating to the use of chlorofluorocarbons (CFCs).**

**Norton Healthcare alleged that the letter was disguised promotion and lacked prescribing information, misled as to exemptions under the Protocol, misled about the banning of CFCs, misled as to the significance of CFC emissions from CFC salbutamol metered dose inhalers (MDIs) and was unbalanced in its reference to the Government's position. Glaxo Wellcome also alleged that prescribing information had been omitted and alleged that the letter misled about the requirements for a Technologically and Economically Feasible Alternative (TEFA), that it referred to CFC emissions from MDIs in an alarmist manner that 3M had failed to substantiate its suggestion that doctors were looking for guidance from the NHS and that the letter misled on the Government's position.**

**The Panel did not consider that the letter was disguised promotion. It was clearly promotional and was in breach as it lacked prescribing information. The Panel considered that the letter was misleading in relation to exemptions for MDIs and was inaccurate in relation to a reference to a ban on the production of CFCs. Breaches of the Code were ruled in relation to these points. The Panel did not consider that the Code had been breached in relation to the other allegations.**

**Norton Healthcare accepted the Panel's rulings. Glaxo Wellcome appealed the rulings of no breach. The Appeal Board noted that 3M Healthcare did have an advantage as its CFC free MDI, Airomir, had been early on the market. It was not unreasonable for 3M to make use of that fact for promotional purposes. The Appeal Board considered that certain aspects could perhaps have been better explained in the letter but supported the Panel's view that the Code had not been breached in relation to the matters under appeal.**

Norton Healthcare Limited (Case AUTH/454/8/96) and Glaxo Wellcome UK Limited (Case AUTH/459/8/96) complained separately about a letter which 3M Health Care Limited had sent to pharmaceutical and medical advisers, directors of public health and chief executives of health authorities. The letter concerned the Airomir inhaler, a 3M product, and the Montreal Protocol, which was an agreement to control the use of chlorofluorocarbons (CFCs).

### CASE AUTH/454/8/96

### COMPLAINT

Norton said that the letter was a promotional item which clearly promoted the Airomir inhaler. There was an obvious breach of Clause 10.1 of the Code as it had been sent out in the guise of a *bona fide* letter of factual information.

Norton was concerned that this type of promotion, and others that 3M Healthcare had undertaken in the past, were misleading, non-factual in content, and unbalanced. The consequence of these tactics was to force health professionals through subtle scaremongering into prescribing, or influencing the prescribing of, Airomir for the treatment of asthma.

### Essential use exemptions for metered dose inhalers (MDIs)

3M stated in the second paragraph of the letter that metered dose inhalers (MDIs) were given temporary exemption until a technologically and economically feasible alternative (TEFA) existed. This statement implied that MDIs were only given an exemption to the Montreal Protocol's ban on the use of CFCs until a TEFA was available. Both the statement and its implications were inaccurate. MDIs for the treatment of asthma and chronic obstructive pulmonary disease (COPD) currently had exemptions until 31 January 1997. The International Pharmaceutical Aerosol Consortium (IPAC), of which 3M (along with Norton) were members, were involved in various meetings throughout 1996 with the parties to the Montreal Protocol to agree a further exemption until the end of 1998. The current exemption was not dictated by or based on the existence of a TEFA (in fact, on the contrary). Moreover, exemptions had not been, in any way, modified as the result of the availability of a TEFA such as Airomir. It was Norton's opinion therefore that 3M was in breach of Clause 7.2 of the Code by misleading the reader by implying that essential use exemptions were only given until such time as a TEFA was available. The launch of Airomir in 1995 did not stop the Montreal Protocol giving MDIs an extension to essential use exemption for 1997.

There were two other examples of how this second paragraph breached Clause 7.2 of the Code. Firstly, the first sentence which stated that "products using chlorofluorocarbons (CFCs) were banned in the European Union at the end of 1994." This was incorrect, misleading and somewhat alarmist. The fact was that products were not banned; the parties to the Montreal Protocol agreed a total phase out of CFC production. Norton's point was that there was a major difference between a ban on products and a ban on the production of CFCs. Secondly, in the final sentence which addressed this issue of essential use exemptions, the letter stated that MDIs were temporarily exempted from the Montreal Protocol's ban on CFCs until a TEFA existed. This clearly implied that the exemption for MDIs was in the past tense when, in real terms, the exemption still existed and would continue to exist until the Montreal Protocol ruled otherwise. The use of the word `were' was therefore inappropriate in that

it misled and was therefore a further breach of Clause 7.2.

### Prescribing information

As the letter was clearly a promotional item it should contain prescribing information. A breach of Clause 4.1 was alleged.

### Atmospheric ozone depletion caused by CFCs

The first sentence of the second paragraph commented that 376 tonnes of CFCs were emitted last year from CFC salbutamol MDIs. This figure of 376 tonnes was only a very small percentage of the total quantity of CFCs which were emitted during 1995 and was therefore misleading as to its significance. A breach of Clause 7.2 was alleged.

The second sentence was also in breach of Clause 7.2 by highlighting that "These emissions add to the existing burden of CFCs and will contribute to ozone depletion." As CFCs for use in MDIs contributed to less than 5% of ozone depleting substances, it was misleading and unbalanced to suggest that emissions from MDIs constituted a "burden" when referring to ozone depletion.

The letter went on to state that "It has been demonstrated that ozone depletion gives rise to an increased level of ultra violet light (UV-B) reaching the earth's surface. An increase in this UV-B radiation has been linked to increased risk of skin cancers and cataracts." These two sentences, by following the statements on the amount of CFCs emitted by MDIs and the "burden" of CFCs on ozone depletion, misled as to its significance, and hence implied that to CFCs were largely attributable the serious medical conditions of skin cancers and cataracts. The use of the word "burden" in this context was also an exaggeration and therefore a breach of Clause 7.8 of the Code.

### Asking the reader to support the Government by encouraging the use of CFC free MDIs

The penultimate paragraph to the letter was an encouragement to prescribe by suggesting that the reader should support the Government. The Government had a commitment to the Montreal Protocol. However, as the parties to the Protocol had agreed to give MDIs essential use exemption (currently until 1 January 1998), equally the Government also had a commitment to CFC containing MDIs until such time as the Montreal Protocol no longer gave exemptions to CFC MDIs. It was therefore unbalanced for 3M to suggest that the Government was only committed to encouraging the use of CFC free MDIs and a further example of a breach of Clause 7.2.

The numerous points noted as potential breaches of the Code were particularly alarmist in nature especially when one bore in mind that the MDI was a vital therapeutic option for the millions of patients worldwide who suffered from asthma and other respiratory disease. Airomir was only one of almost 70 MDIs which would need to be reformulated to a CFC-free alternative. The next few years would hopefully see the introduction of many more CFC-free MDIs. However, in the meantime, the most desirable outcome was a seamless transition to the use of CFC-free inhalers. It was therefore essential to allay any concerns that health professionals might have about CFC MDIs which really had very little effect on ozone depletion. It was irresponsible for 3M to behave in this manner and to mislead health professionals into thinking that CFC MDIs were dangerous and problematic both environmentally and to the patient.

In real terms CFC usage had decreased substantially over the last ten years (to a level a quarter that of 1986). It would be believed from 3M's letter, however, that CFC usage for MDIs was still at the high levels that were seen in the 1980s. There were many other points which should be explained in a more balanced perspective so as not to be alarmist to the proposed reader.

## RESPONSE

3M Health Care Limited said that its promotions of this mandatory transition were both responsible and accurate. The recipients were health authority personnel who would need to implement the change to non CFC inhalers in the coming years. The transition was a major task with over 18 million salbutamol inhalers used annually in the UK by several million asthmatics. With this large and increasing number of inhaler users, such a changeover strategy had huge implications for patients and the NHS. 3M had presented the wider picture of the problem, so that health professionals were better able to understand the global driving forces behind the replacement of CFCs in MDIs.

The International Pharmaceutical Aerosol Consortium (IPAC) had proposed a transition policy to the United Nations Environmental Protection Agency (UNEP) that committed companies, in good faith, to encourage acceptance of non-CFC products and to educate both doctor and patient about the transition. 3M supplied the latest UNEP report, the appendices outlining the IPAC transition policy for MDIs, and, for further information, a statement from a key patients advocacy group, the British Lung Foundation.

3M supplied an original copy of the letter the subject of complaint and a document headed "CFC-Free Transition" which consisted of answers to common questions as it appeared in its approvals documentation. 3M understood that the prescribing information was not included during final word processing and merging. The letter was sent to approximately 484 recipients who were pharmaceutical and medical advisers, directors of public health and chief executives of health authorities. 3M accepted that the lack of prescribing information was in breach of the Code. The company apologised and gave an undertaking that this would not be repeated in the future.

In response to the specific allegations the company commented as follows:

### Norton Healthcare claimed that 3M was incorrect in implying that essential use exemptions were only given until such time as a TEFA was available

3M referred to the Official Journal of the European Communities, Commission Decision of 26 July, 1995. The use of a controlled substance (in this case CFCs) should qualify as "essential" only if "there are no available technically and economically feasible alternatives or substitutes". 3M also supplied the Official Journal of the European Communities notice of 25 June, 1996 that

provided the detail for application for essential uses. Clearly, this process required annual nominations. 3M also referred to a confidential letter from the Congress of the United States House of Representatives to the FDA on 28 June, 1996, stating that "some CFC uses were granted a temporary exemption from the ban on CFCs until alternatives became available". Clearly it was a common understanding that this exemption was temporary. While Norton argued that the availability of a TEFA had not yet influenced the essential use exemptions, it was quite obvious that this was the intent of the legislation.

**Products using chlorofluorocarbons were banned in the EU**

The intent of this paragraph was to inform the recipients of the consequences of the Montreal Protocol. Norton was correct in its observation that it was the production of CFCs for non-essential use products that was banned. However, 3M did not believe that this statement was alarmist or essentially misleading. For example, CFC driven nasal aerosols had been withdrawn from the UK market. These were rapidly discontinued following the CFC ban. The ban on manufacture of CFCs led inexorably and rapidly to a cessation of manufacture of the actual product.

**The use of the word "were" in conjunction with temporary exemptions**

The use of the phrase "were temporarily exempted" was correct in the sentence's context. At the time of the CFC Manufacturing ban in the EU in 1994, there were temporary exemptions.

**The significance of the tonnage of CFCs released from salbutamol MDIs was misleading**

No intimation of the significance of the release of 376 tonnes of CFCs from salbutamol MDIs was made. The estimate was only intended to give a reasonable view of the tonnage of CFC release that could be reduced by a move to non-CFC salbutamol inhalers. 3M referred to a confidential letter to the FDA from the Centre for Global Change dated 24 June, 1996, which argued that many specialised applications of CFC use had already been subject to regulation and that failure to regulate the use of CFCs in MDIs might have consequences for human health, especially with the growth of asthma and chronic respiratory diseases. Furthermore, concern was expressed that any delay in removing exemptions would undermine the message on the importance of industry commitment to environmental leadership and investment.

**It was misleading and unbalanced to suggest that emissions from MDIs constituted a burden**

The wording was clear and stated that CFCs from MDIs added to an existing CFC burden, and were not themselves the sole cause of the burden. More than 95% of the 1996 European allocation of CFCs was for use in the manufacture of MDIs.

**The use of the word "burden" was an exaggeration**

Again the use of the word burden applied clearly to the total CFC load affecting the ozone layer and was not an exaggeration. This was a serious public health issue and 3M considered that Norton was attempting to minimise its significance in order to maintain and grow its current CFC franchise at the expense of environmental considerations

**It was unbalanced for 3M to suggest that the Government was only committed to encouraging the use of CFC free MDIs**

There was no reference or suggestion in the 3M letter that the Government was only committed to encourage the use of CFC free MDIs. The letter asked for the recipients' support for the Government's commitment to the Montreal Protocol. As a signatory to the Montreal Protocol, the UK Government was committed to the phase out of products containing CFCs. Its continuing commitment to the Montreal Protocol was evident in the announcement by the Minister of Health of the target for the specific phase out of CFCs from MDIs by 1999, as reported in Hansard 8 July, 1996.

**RULING**

The Panel noted that 3M accepted that the letter should have included prescribing information for Airomir and had said that the omission had occurred in error. A breach of Clause 4.1 of the Code was ruled. The Panel considered that the letter was clearly promotional in nature and not disguised promotion as alleged and ruled that there had been no breach of Clause 10.1 of the Code.

The Panel observed that there was no mechanism for approving inhalers to be technologically and economically feasible alternatives (TEFAs) to inhalers using CFCs and that there was no official definition of what exactly a TEFA was. It seemed to the Panel, however, that it was reasonable to regard Airomir as a TEFA. That being so, and 3M being early on the market with such a product, it was not unreasonable for 3M to make use of that feature for promotional purposes. The question to be considered was whether, in so doing, 3M had misled as to its significance or as to the factual background.

The Panel noted that although there were temporary exemptions to the Montreal Protocol, its objective was to eliminate the use of CFCs. The Panel was of the opinion that the letter did give the impression that the Montreal Protocol gave exemption to MDIs only until such time as a TEFA existed, with the implication that now that one did exist the exemption was spent. This was not true as, according to Norton, MDIs for asthma and chronic obstructive pulmonary disease had exemption until 31 January 1997 with the possibility of the exemption being extended until the end of 1998. The Panel ruled that the letter was misleading in this regard and in breach of Clause 7.2 of the Code. The reference to a "ban" on the production of CFC was factually inaccurate and was also ruled to be in breach of Clause 7.2.

The Panel did not consider that either the reference to the emission of 376 tonnes of CFCs last year from salbutamol MDIs or the use of the word "burden" or the reference to cancer and cataracts were in breach of the Code. It could

be argued that there was over emphasis but most people would look at the matter from the same perspective as the letter. The amount was not an insignificant one, even if it was only a small proportion of total CFC emissions.

The Panel noted that a statement issued by the British Lung Foundation, supplied by 3M, explained that production of CFCs had ceased in the European Union apart from specific uses of which MDIs were the largest. It further stated that the exemption was necessary in the short term but the British Lung Foundation supported the research efforts which were leading to alternatives and that it would be important to convert to the new products as they became available. The Minister of State for Health had said, according to the Hansard report provided by 3M, that the Medicines Control Agency was complying with the European Regulations and the Montreal Protocol concerning the removal of CFC propellants from the environment which undertook to remove CFCs from all medicinal products by the end of 1999. The Minister further stated that no guidance had been issued to doctors regarding non CFC inhalant medication although factual material was included in a Medicines Resource Centre bulletin in September, 1995. The Government was committed to the removal of CFCs from all medicinal products by the end of 1999.

The Panel did not consider that the letter breached the Code in relation to what it said about the Government's position and ruled no breach of the Code in that regard.

* * *

Norton accepted the Panel's rulings of no breach. 3M Health Care accepted the Panel's rulings of breaches of Clauses 4.1 and 7.2 of the Code.

**CASE AUTH/459/8/96**

**COMPLAINT**

Glaxo Wellcome UK Limited said that the letter from 3M Healthcare Limited regarding its Airomir inhaler misled readers and was in breach of several clauses of the Code. Glaxo Wellcome's complaints were as follows:

### 1 Promotional letter without prescribing information

A breach of Clause 4.1 of the Code was alleged as there was no prescribing information for Airomir.

### 2 Technologically and Economically Feasible Alternative (of the Montreal Protocol)

In the third paragraph, 3M expressed confidence that the requirements for a Technologically and Economically Feasible Alternative (TEFA) had been met. The Montreal Protocol did not define what a TEFA was, and, in addition, the Protocol made no provision as to a transitional strategy. Further, the UN Technical Environmental Assessment Panel (TEAP) had been looking at a transitional strategy and would recommend one to the parties to the Protocol, for endorsement, at a meeting to be held in November, 1996.

Thus, Glaxo Wellcome alleged that this was misleading in breach of Clause 7.2 of the Code.

### 3 Linking 376 tonnes of CFC emission in 1995 (in the UK) to increased risk of skin cancers and cataracts

Glaxo Wellcome was particularly concerned by paragraph four of 3M's letter. Many companies had been developing CFC-free MDIs. 3M made no reference to the fact that once in the atmosphere CFC containing propellants lasted for a great length of time (CFC 11 for 75 years, CFC 12 for 111 years and CFC 14 for 185 years). In the early 1990's over one million tonnes per year of CFCs were being produced worldwide. The tiny contribution made by MDIs to the total atmospheric burden compared with other much larger sources of CFCs, while regrettable, had been taken out of context in an alarmist way which Glaxo Wellcome considered brought disrepute to other MDI manufacturers. A breach of Clause 7.2 was alleged.

### 4 "Our experience indicates that doctors are looking for direction from the NHS..."

This sentence suggested that doctors look to the NHS for direction in their prescribing habits, while for the NHS the sensible approach was to encourage doctors to switch to Airomir now. Glaxo Wellcome had asked 3M for all the evidence to support its assertion but had failed to receive either a satisfactory response or any substantiating evidence.

A breach of Clause 7.4 was alleged.

### 5 "Please support the Government's commitment to the Montreal Protocol..."

Glaxo Wellcome considered this paragraph misled recipients by suggesting that support for Airomir would be in line with the Government's commitment to the Protocol. By inference, it was suggesting that the use of CFC containing inhalers was therefore against the Government's policy. This was not the case. The remaining aerosol producing companies in the UK were actively seeking to agree a smooth, speedy and seamless transition strategy to CFC-free MDIs. Breaches of Clauses 7.2 and 8.1 were alleged.

**RESPONSE**

### 1 Promotional letter without prescribing information

3M acknowledged that its letter did not contain prescribing information.

### 2 Technologically and Economically Feasible Alternative (of the Montreal Protocol)

The 3M letter stated that 3M was confident that the requirements for a TEFA had been met. Whilst agreeing that a formal definition of a TEFA was not yet defined, 3M pointed out that:

a The Airomir product was acknowledged by the Technical and Economic Assessment Panel of the United Nations Environmental Protection Agency and it reported that, for the first time it was able to report with confidence that it should be feasible to eventually

commercialise alternatives to the commonly used CFC MDIs. TEAP clearly saw Airomir as a TEFA.

b The BP Commission had confirmed its intent to extend the existing monograph on salbutamol pressurised inhalation to include salbutamol sulphate and non-chlorofluorocarbon propellants at the earliest convenient opportunity. The BP Commission clearly saw Airomir as a technically feasible alternative.

c The price of Airomir was in line with the PPRS request for a price equivalent to the existing CFC price. 3M would argue that this defined Airomir as an economically feasible alternative.

Based on these acceptances, 3M considered that Airomir was an environmentally, technically and economically feasible alternative to CFC salbutamol MDIs.

### 3 Linking 376 tonnes of CFC emission in 1995 (in the UK) to increased risk of skin cancers and cataracts

The estimate that 376 tonnes of CFCs from salbutamol MDIs were released into the atmosphere in 1995 was only intended to give a reasonable view of the tonnage of CFC release that could be reduced by a move to non-CFC salbutamol inhalers. 3M referred to a confidential letter to the FDA from the Centre for Global Change dated 24 June, 1996, which argued that many specialised applications of CFC use had already been subject to regulation and that failure to regulate the use of CFCs in MDIs might have consequences for human health, especially with the growth of asthma and chronic respiratory diseases. Furthermore, concern was expressed that any delay in removing exemptions would undermine the message on the importance of industry commitment to environmental leadership and investment. The 3M letter was sent out to strategic planners within the NHS in order that they might assess the wider implications of the aims of the Montreal Protocol and the magnitude of the public health threat that continued CFC emissions posed. 3M was, therefore, stating facts which, though they might be alarming, were informative.

### 4 "Our experience indicates that doctors are looking for direction from the NHS..."

Feedback to 3M via its representatives and key accounts managers clearly indicated that doctors were indeed looking for leadership and guidance to manage the transition to non-CFC inhalers. The 3M letter encouraged the use of non-CFC inhalers through the development of guidelines and by prescribing advice, that was, to create, develop and manage transition strategies. It did not encourage a specific product switch.

### 5 "Please support the Government's commitment to the Montreal Protocol..."

The 3M letter clearly encouraged the development of transition strategies (guidelines and prescribing advice) to support the Government's commitment to the Montreal Protocol and in no way suggested that support for any specific product would support Government strategy. This appeared to have been deliberately misconstrued by the complainant. Should the complainant be in any doubt about the Government's continuing support for early phasing out of CFCs, 3M referred to a recent report in Hansard. There was absolutely no intent to disparage other CFC MDI products.

## RULING

The Panel considered that certain of its rulings in Case AUTH/454/8/96 similarly applied in this case.

### 1 Promotional letter without prescribing information

The Panel noted that it had already ruled in Case AUTH/454/8/96 that there had been a breach of Clause 4.1.

### 2 Technologically and Economically Feasible Alternative (of the Montreal Protocol)

The Panel did not accept that the letter was misleading in relation to 3M's statement that the requirements for a TEFA had been met. As in Case AUTH/454/8/96, notwithstanding the lack of any approval mechanism or definition in relation to a TEFA, it seemed reasonable to regard Airomir as being a TEFA.

### 3 Linking 376 tonnes of CFC emission in 1995 (in the UK) to increased risk of skin cancer and cataracts

The Panel had already ruled in Case AUTH/454/8/96 that the reference to 376 tonnes of CFCs and to increased risk of cancer and cataracts was not in breach of the Code.

### 4 "Our experience indicates doctors are looking for direction from the NHS..."

This allegation had not been made in case AUTH/454/8/96. The Panel considered that this statement was setting out the company's experience rather than stating a fact which could be substantiated by normal means. The subject was one of general interest and the statement seemed to the Panel to be a reasonable one. No breach of Clause 7.4 was ruled.

### 5 "Please support the Government's commitment to the Montreal Protocol..."

The Panel had already ruled in Case AUTH/454/8/96 that references to the Government's position were not in breach of the Code.

## APPEAL BY GLAXO WELLCOME

### 2 Technologically and Economically Feasible Alternative (of the Montreal Protocol)

Glaxo Wellcome said that 3M had clearly suggested that its Airomir product was a TEFA for all salbutamol containing MDIs. It suggested in its letter that steps should be taken to encourage clinicians to prescribe Airomir now. Whilst 3M might well have done bioequivalence studies for its own CFC containing MDI and against Ventolin, Glaxo Wellcome was unaware that

similar work had been done for other salbutamol containing aerosols propelled by CFCs. Indeed, 3M in its defence agreed that a formal definition of a TEFA had not yet been defined. Only the parties to the Montreal Protocol, meeting in plenary session, had the locus to decide what constituted a TEFA, and this had not yet been done. The Code of Practice Authority had no locus to rule on this.

There were several other important criteria missing from 3M's proposed definition for a TEFA, for instance:

Therapeutic indications - two products with different therapeutic indications could not necessarily be considered alternatives. Under 3M's proposal a new MDI product could force off the market existing MDIs with a broader range of therapeutic indications. Patients using the existing MDIs for one of the "lost" indications would be denied treatment when these existing MDIs were pulled from the market.

Dosage strength - the vast majority of existing MDIs were offered in more than one dosage strength. Physicians used these dosage options to prescribe treatment tailored to the individual needs of their patients. If 3M's proposal was adopted, a CFC-free MDI with fewer dosage strength options could replace an existing CFC MDI, thereby restricting physician choice and patient access to needed treatment options.

Risk benefit ratio - Each MDI product on the market had a unique ratio of patient risk to patient benefits. Generally speaking, the lower the risk benefit ratio the better the product was for the patient. Under 3M's proposal a non-CFC MDI with a higher risk: benefit ratio could force off the market CFC MDIs with considerably lower risk: benefit ratios. This would obviously not be in the patient's interest.

Although not specifically a Code of Practice matter, of undoubted importance were the following two points:

Possible breach of the Treaty of Rome 1957 - Unilateral action by national governments might put those countries in breach of the Treaty of Rome 1957. Glaxo Wellcome understood that to be the position of the UK Department of Trade and Industry. It would also infringe GATT and WTO agreements. Glaxo Wellcome would be surprised if the Code of Practice Panel and Her Majesty's Government were to be divergent on this issue.

Monopoly - For one manufacturer to be granted a monopoly position would potentially damage a huge section of the pharmaceutical market, removing price competition and potentially jeopardising security of supply. It could well seriously alarm many patients who had come to rely on branded inhalers from other sources, who might be sensitive to new excipients, and for whom there would also need to be much preparatory education around the introduction by those companies of their CFC-free alternatives. Some companies, including Glaxo Wellcome had already started this programme.

With the exception of 3M, the remainder of the aerosol producing community in Britain agreed that the best way to ensure patient access to vital aerosols was through the seamless transition to non-CFC containing replacements. This was in complete contrast to 3M's policy of wishing to encourage wholesale change from all salbutamol containing MDIs to its own CFC-free product. This would appear to be the basis for 3M's inappropriate suggestion that its product, Airomir, therefore represented a TEFA for all salbutamol containing MDIs.

### 3 Linking 376 tonnes of CFC emission in 1995 (in the UK) to increased risk of skin cancers and cataracts

Glaxo Wellcome was particularly concerned about the alarmist, misleading and unbalanced comments made by 3M with regard to the continued emission of CFCs. Glaxo Wellcome, along with many other aerosol manufacturers, had spent many millions of pounds in vigorously pursuing CFC-free alternatives. Glaxo Wellcome was fully committed to supporting the phased introduction of these. Glaxo Wellcome strongly rejected 3M's assertion that "any delay in removing exemptions would undermine the message on the importance of industry commitments to environmental leadership and investment". Glaxo Wellcome believed that the British pharmaceutical industry had very clearly demonstrated its commitment to support this environmentally determined switch. However, neither in its letter nor in its response to the Panel had 3M acknowledged the enormous CFC burden that was already in the atmosphere. The vast majority of this of course had been contributed by sources other than medicinal aerosols. Glaxo Wellcome strongly rejected 3M's suggestion that a carefully planned and seamless transition by aerosol manufacturers to CFC-free alternatives in any way undermined the industry commitment to environmental leadership.

Glaxo Wellcome strongly supported the Code of Practice and believed therefore, that claims made in promotional literature should provide "accurate, balanced, fair, objective and unambiguous information and must be based on an up to date evaluation of all the evidence and reflect that evidence clearly". Glaxo Wellcome believed that 3M's intention, and this letter in particular, misled NHS planners about the implications of the small fraction of CFCs that were still adding (albeit regrettably) to the environmental burden.

### 4 "Our experience indicates that doctors are looking for direction from the NHS ...."

Glaxo Wellcome considered that 3M, whether making a claim or setting out its experience, was still bound by the Code. Glaxo Wellcome requested substantiation and this was not received. If 3M had used the argument in its response that this reflected feedback, then Glaxo Wellcome would perhaps have accepted that substantiation. However, it failed to provide this substantiation and therefore Glaxo Wellcome alleged that 3M was in breach of the Code.

### 5 "Please support the Government's commitment to the Montreal Protocol ...."

Once again, 3M had presented an unbalanced view of the situation. The Government had signed up to the Montreal Protocol and indeed in the Hansard report provided by 3M, the Government was committed to removing CFC from medicinal products by the end of 1999. Further, Paragraph 2.2 of the Technical and Economic Assessment

Panel's Report of June 1996 stated that "It is likely that CFC MDIs will be virtually eliminated in non-Article 5(1) countries no later than 2005 ....". The UK is a non-Article 5(1) country. 3M did not mention either of these facts in its letter sent out in June 1996. Neither did 3M balance its reflections on Government policy by confirming that the Government was in the process of granting exemptions for 1997 and would soon be considering them for 1998 and 1999. This would suggest that the Government was thinking carefully about how best to phase in the new CFC-free propellants in a responsible fashion and one which Glaxo Wellcome strongly supported.

In conclusion, Glaxo Wellcome believed that 3M had not presented a balanced view of the political and regulatory situation regarding the transition to CFC-free containing propellants. Indeed, in its response it had quoted the Government as "looking to phase out CFC containing propellants by the end of 1999". To send its letter out in June 1996 without acknowledging the timetable the Government was currently considering, was misleading.

**RESPONSE FROM 3M HEALTH CARE**

## 2 Technologically and Economically Feasible Alternative (of the Montreal Protocol)

3M said that it was confusing in that Glaxo Wellcome asked the Authority to rule that 3M's statements were misleading. Glaxo Wellcome stated its belief that the Code of Practice Authority "has no locus to rule on this", despite appealing the Panel's ruling.

3M believed its comments were perfectly acceptable, and in response to Glaxo Wellcome's additional arguments it pointed out that:

i Glaxo appeared to be using the definition of a TEFA as that of exact equivalence. The wording used was "alternative". The Commission of the European Communities, Rules governing Medical Products Vol III - addendum II, May 1992, stated that they were ".... alternatives if they contain the same therapeutic moiety but differ in chemical form of that moiety or in the dosage form or strength".

ii 3M did not state "all" salbutamol MDIs.

iii 3M wished to emphasise the TEAP report that stated "The TOC is pleased to report that industry's research and development has proceeded well. The schedule for the safe introduction of new propellants and reformulated products suggested in the 1993 Report of the Aerosols TOC still appeared to be on target, with the first reformulated version of salbutamol, 3M's Airomir, being approved in 21 countries with more approvals expected this year. For the first time the TOC was able to report with confidence that it should be feasible to eventually commercialise alternatives to most of the commonly used CFC MDIs".

3M believed this implied that TOC appeared to be more confident with the arrival of Airomir that a TEFA had been met.

iv Glaxo Wellcome provided no evidence that a TEFA had not been met. Its arguments included:

a Different indications - 3M's previous comments on "alternative" appeared to address this. In addition Glaxo Wellcome had not stipulated which indications it was referring to, for which it had regulatory approval and essential use exemptions. Nasal inhalers for rhinitis were discontinued as they were not "essential use" exempted. Similarly 3M's own Medihaler EPI (adrenaline) was not exempt for essential use, despite an indication for anaphylactic reactions. The alternative was an injection product which was a long way from the minor aerosol differences that Glaxo Wellcome claimed to be so important.

b Dosage strength - Again this was a trivial argument. Firstly, the definition of alternative allowed for different strengths. Secondly, the difference in efficacy between one puff and two puffs of 100mg was small. Lastly, for salbutamol, the dose per puff appeared to be 100mg in all UK salbutamol MDI formulations.

c Risk Benefit Ratio - Glaxo Wellcome provided no evidence for a different risk-benefit ratio between CFC and non-CFC salbutamol products. 3M believed it had provided the MCA with evidence to support a similar risk-benefit ratio between Airomir and Ventolin. In fact some of the Airomir data on inhaler performance at low temperatures, and its superior performance in the pharmaceutical areas of loss of prime and end of can dosing, would suggest a technologically more advanced product than current CFC salbutamol inhalers including Ventolin. Clinical data, on file with 3M, showed that the risk benefit ratio of Airomir was at least equivalent with that of Ventolin over 1 year in a randomised study in 190 patients.

d Treaty of Rome - 3M understood that international treaties took precedence over national laws. 3M also believed Her Majesty's Government would not put national agreements at risk or ignore such specifics.

e Monopoly - 3M wished to assert very strongly that it was not aware that Glaxo Wellcome had any remit to speak for the rest of the industry. 3M was developing twelve different CFC-free products for seven different companies. Glaxo Wellcome's assertion that "the remainder of the aerosol producing community in Britain" reflected an industry viewpoint was not correct.

While Glaxo Wellcome might, like 3M, wish to promote a seamless transition in the interest of patient welfare and the environment, this did not mean protecting Glaxo Wellcome's dominant position or market share. There were 17 bronchodilator products on the UK market. Not all were salbutamol, and many of them were not MDIs. Anyone was free to enter the market with CFC-free salbutamol MDIs. No monopoly existed. If it was an issue it was one for the Government to address.

## 3 Linking 376 tonnes of CFC emission in 1995 (in the UK) to increased risk of skin cancers and cataracts

Glaxo Wellcome, along with other manufacturers, might be committed to developing alternatives. However such commitment had not yet produced a Glaxo Wellcome salbutamol CFC-free product, some 21 months after 3M launched Airomir in the UK. The point was that an

alternative CFC-free salbutamol MDI was available today and that promotion of this alternative was the commercial prerogative of the technology leader.

3M supplied a recent World Health Organisation report that estimated the additional cataracts and melanomas from the decline in ozone/increase in UV.

The issue was that it was responsible to inform health professionals of the health consequences of ozone depletion, and that these health concerns were why the Montreal Protocol existed. The tonnage from salbutamol MDIs was a clear and legitimate fact. Glaxo Wellcome's assertions that this was unbalanced, was an attempt to prevent 3M from providing the facts to health professionals. 3M neither claimed nor suggested that the 376 tonnes of CFC emissions that could be saved now were related to skin cancer rates. This was a public health issue and the facts must be clearly disseminated.

### 4 "Our experience indicates that doctors are looking for direction from the NHS...."

A summary of the results from some qualitative research on this issue was provided. 3M could also provide excerpts from representative reports, but regarded this type of information as anecdotal in an isolated form. 3M would expect a reasonable response would be to accept its summary of representatives' remarks previously provided. 3M regarded this statement to be perfectly reasonable and that sufficient substantiation was provided.

### 5 "Please support the Government's commitment to the Montreal Protocol ..."

Glaxo Wellcome's comments in its appeal letter were unbalanced. Glaxo Wellcome failed to mention that TEAP also stated "a major reduction in CFC use for MDIs (can be made) by the end of the year 2000", and "that these dates can be reviewed annually to accelerate the schedule".

Glaxo Wellcome also declined to add that in the process of granting exemptions the TEAP could review the essential use exemptions and reallocate or destroy surplus rendered unnecessary as a result of technical progress or market adjustments. Excerpts from the Handbook for UNEP that stated this were provided.

Glaxo Wellcome could not deny that the Government were committed to this transition.

In summary, 3M believed that Glaxo Wellcome's concerns were commercial. 3M believed Glaxo Wellcome was using the Code of Practice as a commercial tool and it was Glaxo Wellcome's actions in this appeal that were irresponsible. Glaxo Wellcome showed no concern for the environmental issue at hand. Recent press examples from Australia and the UK which were supplied pointed to Glaxo Wellcome opposing this CFC transition.

## FURTHER COMMENTS FROM THE COMPLAINANT

### 2 Technologically and Economically Feasible Alternative (of the Montreal Protocol)

Glaxo Wellcome reiterated its complaint as in its first letter. The crux of Glaxo Wellcome's case was that it believed 3M had provided misleading information on two counts namely:

- The statement that 3M were confident that the requirements of the Parties to the Montreal Protocol for a TEFA had been met, when no agreement on the definition of a TEFA had been achieved.
- The misleading information that CFCs in MDIs for the treatment of asthma and COPD *were temporarily* exempted from the ban.

The parties to the Montreal Protocol had not discussed to date the definition of a TEFA, or indeed the processes that should be adopted to define a TEFA. While 3M Healthcare had been granted a licence for Airomir as a CFC-free presentation of salbutamol, it was misleading to attempt to imply that this defined the title of TEFA, as if it was endorsed by the Montreal Protocol, which it was not. Furthermore, the United Nations Technology and Economic Assessment Panel (TEAP), and the Aerosol Technical Options Committee (ATOC) which was the worldwide panel of experts had not recommended a definition of a TEFA and were currently in the process of reviewing the CFC-transition in order to make recommendations to the Parties of the Montreal Protocol.

3M had stated that CFCs were banned, however, "some products were considered essential, such as MDIs for asthma, and were temporarily exempted from this rule". This use of the past tense was misleading and implied that there were no further exemptions for CFCs in metered dose inhalers (MDIs). CFC requirements for MDIs were and continue to be, reviewed annually, and indeed the relevant regulatory authorities had already begun the process of allocating CFCs for exempted use for 1999.

It was therefore misleading to suggest that no further exemptions for CFCs in MDIs were being granted, and furthermore this inferred that it was because 3M had met the requirements for the definition of a TEFA.

The TOC report stated "that it should be feasible to eventually commercialise alternatives .....". Glaxo Wellcome strongly disagreed with 3Ms conclusion that "this implies that TOC appear to be more confident with the arrival of Airomir that a TEFA has been met", as there has been no definition of a TEFA, no one could be sure that 3M could meet it.

### 3 Linking 376 tonnes of CFC emission in 1995 (in the UK) to increased risk of skin cancers and cataracts

Glaxo Wellcome would not wish to restrict any fair and legitimate promotional activities carried out by 3M.

Glaxo Wellcome was not suggesting that health professionals should not be informed about the consequences of ozone depletion. However, it was concerned that 3M failed to put the small increase in environmental ozone depletion into context. It was a known fact that total annual world production of CFCs peaked in 1987 at just over one million tonnes. CFCs and MDIs had always been a small fraction of the total CFC usage. World CFC usage in MDIs at the peak of CFC production accounted for less than 0.08% of the total usage.

Scientific calculations had shown that exemption to continue using CFC in MDIs between 1995 and the year 2000 would not have any detectable affect on the rate of ozone depletion or recovery. Some readers might infer from their letter that even this small amount might have a significant impact on the amount of ultra violet B reaching the earth's surface and therefore increase the risk of skin cancers and cataracts. Whilst each sentence of the paragraph was correct, the juxtaposition of such information might mislead some readers.

### 4 "Our experience indicates that doctors are looking for direction from the NHS..."

Clearly this question of substantiation was overlooked in 3M Health Care's letter. However, Glaxo Wellcome accepted the Panel's view that it would have been difficult to provide substantiation in the customary manner.

### 5 "Please support the Government's commitment to the Montreal Protocol..."

The Technology and Economic Assessment Panel (TEAP) sought "a major reduction in CFC use for MDIs by the year end of the year 2000". Glaxo Wellcome was working with many other aerosol manufacturers in the International Pharmaceutical Aerosol Consortium (IPAC) to ensure that this indeed did happen. Glaxo Wellcome believed that the Government, within the TEAP stated time frame, would wish to ensure that all the companies achieved a seamless transition for their products within the stated time frame, or their CFC-free alternatives were developed and approved. Glaxo Wellcome was aware that the Government was committed to this form of transition.

In summary, there were many complex issues which would govern a successful transition to CFC-free MDIs. There were worldwide expert panels appointed and operating under the auspices of the Montreal Protocol to propose strategy for transition, appropriate definitions (including the definition for a TEFA), and appropriate processes for introduction of CFC-free products and ultimately for phase-out of CFC containing MDIs. It was the signatory parties to the Montreal Protocol who would debate and approve these proposals, and incorporate them into legislation.

Glaxo Wellcome considered that it was for these worldwide expert panels to debate the CFC-transition for MDIs, and it was not for pharmaceutical companies or the Code of Practice Authority to prejudge aspects such as the TEFA definition.

### APPEAL BOARD RULING

The Appeal Board noted that the letter did not advocate changing all patients on salbutamol to Airomir. The recipients of the letter (pharmaceutical and medical advisers, directors of public health and chief executives of health authorities) were asked to encourage the use of CFC free MDIs through prescribing advice and treatment guidelines. In the Appeal Board's view this was not unreasonable, although the background and transition could perhaps have been better explained in the letter.

The Appeal Board noted that 3M did have an advantage as its CFC free MDI, Airomir, had been early on the market. It was not unreasonable for 3M to make use of that fact for promotional purposes.

Dealing with the specific points:-

### 2 Technologically and Economically Feasible Alternative (of the Montreal Protocol)

The Appeal Board noted that there was no mechanism for approving inhalers to be technologically and economically feasible alternatives (TEFAs) to inhalers using CFCs and that there was no official definition of what exactly a TEFA was. It seemed to the Appeal Board, however, not to have been unreasonable for the Panel to have regarded Airomir as a technologically and economically feasible alternative. The Appeal Board upheld the Panel's ruling of no breach of the Code.

The appeal on this aspect therefore failed.

### 3 Linking 376 tonnes of CFC emission in 1995 (in the UK) to increased risk of skin cancers and cataracts

The Appeal Board noted that this was a factual statement even though it was true that the amount was small in relation to the total atmospheric burden which had largely arisen from other much larger sources of CFCs. Although it was argued that there was over emphasis, the Appeal Board did not consider that the letter was unreasonable in this respect. The Appeal Board upheld the Panel's ruling of no breach of the Code.

The Appeal on this aspect therefore failed.

### 4 "Our experience indicates that doctors are looking for direction from the NHS..."

The Appeal Board noted that, in its final comments, Glaxo Wellcome had accepted the Panel's view that it would have been difficult to provide substantiation in the customary manner in relation to this claim. The Appeal Board shared this view and considered that 3M Health Care had justified its use. The Appeal Board upheld the Panel's ruling of no breach of the Code.

The appeal on this aspect therefore failed.

### 5 "Please support the Government's commitment to the Montreal Protocol..."

The Appeal Board considered that this statement reflected the Government's position in support of the aims of the Montreal Protocol. The Appeal Board upheld the Panel's ruling of no breach of the Code.

The appeal on this aspect therefore failed.

**Case AUTH/454/8/96**

**Complaint received** 14 August 1996

**Case completed** 24 October 1996

**Case AUTH/459/8/96**

**Complaint received** 28 August 1996

**Case completed** 18 December 1996

CASE AUTH/455/8/96

# SEARLE v BOEHRINGER INGELHEIM

## "Dear Doctor" mailing and journal advertisement for Mobic

**Searle complained about a "Dear Doctor" mailing and a journal advertisment issued by Boehringer Ingelheim. Both pieces carried prescribing information for Mobic and said that the product was not yet available.**

**The Panel accepted that it had been established that NSAIDs had different COX-2: COX-1 inhibition ratios and there was some evidence that the difference in the levels of gastrointestinal side effects correlated with this ratio. There was insufficient evidence to establish that this theoretical concept translated into definite clinical benefit. The Panel ruled that the material was misleading and exaggerated and that the claims implied a special merit for Mobic which had not been substantiated.**

**Upon appeal by Boehringer Ingelheim, the Appeal Board upheld the Panel's ruling.**

**The Panel ruled no breach with regard to an allegation that the non proprietary name was not adjacent to the brand name. An allegation regarding the size of the black triangle was not within the scope of the Code.**

Searle complained about two items distributed by Boehringer Ingelheim Limited. The first item was a "Dear Doctor" mailing (ref BIL5136) sent to general practitioners. The mailing consisted of a "Dear Doctor" letter, a large leaflet headed "Test tube baby" and a reply paid card offering a video for oesteoarthitis patients and further information on preferential COX-2 inhibition. Both the letter and the leaflet carried prescribing information for Mobic (meloxicam) and said that the product was not yet available. The second item was a journal advertisement entitled "Test tube baby" (ref BIL5199) which appeared in GP, 16 August 1996.

### COMPLAINT

Searle alleged that both the "Dear Doctor" letter and the leaflet were intended to promote Mobic. Prescribing information for Mobic appeared on both the letter and leaflet. The letter was headed "New beginnings" and opened with a statement "Soon you will be able to distinguish between NSAID treatments in a way previously unknown". In Searle's view, this clearly indicated that a new NSAID with some special, ie distinguishable, properties or merits was about to become available. The third paragraph of the letter qualified these "distinguishable" properties by saying "... with new anti-inflammatory drugs, you may be able to inhibit physiological and inflammatory processes differentially" because, as the letter went on to explain, COX-1 and COX-2 enzymes had different actions. The material was broadly designed to emphasise that preferential COX-2 inhibition was beneficial to patients in terms of "a relatively low risk of ulceration". Searle raised two issues.

### 1 That Mobic was in some way a novel agent in terms of its COX-2:COX-1 inhibition ratio.

Searle said that one of the main implications of the "Dear Doctor" letter and the leaflet was that there was something novel with regard to the COX-2:COX-1 effects of Mobic. The overall impression was that something new, with regard to the properties of Mobic, was going to confer a significant clinical benefit. Searle said there was nothing new about the science and potential clinical implications of the different effects which resulted from inhibiting the two COX enzymes. These were described as long ago as 1991 and all currently marketed NSAIDs showed inhibition to differing degrees of both enzymes. What was still in doubt was the relevance of COX-2:COX-1 ratios, derived from *in vitro* studies, to clinical practice. Searle considered that a quotation from Vane in the leaflet that "... a good relationship is indeed shown between COX-2 selectivity and an improved gastro-intestinal side-effect profile..." was just one personal opinion which was not held by many other experts in the field. This had not to date been verified in the case of Mobic by appropriate clinical studies. Searle alleged that the use of such a statement in relation to Mobic was misleading in breach of Clause 7.2 of the Code. Even if the statement were unrelated to Mobic, it was not truly representative of all the evidence relating to the issue.

The relevance of the COX-2:COX-1 ratio had been the subject of ongoing debate in The Lancet. Bjarnason *et al* had recently stated that "We are sceptical about the relevance of extrapolating these IC50 ratios, derived *in vitro*, to clinical practice". Bennett also made a similar comment on the issue: "It is still too early to decide on the importance of COX-2 selectivity in avoiding damage to the gastrointestinal mucosa". Searle was not aware of any data which had changed this position. The company alleged that the clinical relevance of COX-2:COX-1 ratios derived from *in vitro* studies was still not proven and use of such data was in breach of Clause 7.2 of the Code. Undue weight was given to the *in vitro* data without clinical proof of its clinical significance.

As an example of the potential to mislead, nimesulide, which was also mentioned by Bennett *et al*, was considered to be highly selective in terms of COX-2:COX-1 ratios; however, it was still associated with a significant level of gastroduodenal ulceration in the two published studies of endoscopic effects. The second study showed no significant difference in terms of endoscopic damage between nimesulide and diclofenac, the latter being well defined as causing GI damage. These studies demonstrated the danger of extrapolating from the *in vitro* COX-2 selectivity data to the potential clinical benefits.

There was also debate about the methodology and interpretation of data from *in vitro* assays of COX-2:COX-1 ratios. This issue had been identified in a publication from scientists at Boehringer Ingelheim's department of inflammatory diseases, which stated that "... interpretation and comparison of the results of these studies is complicated by different assay conditions, species and cell types that have been used" (Churchill *et al*). If Boehringer Ingelheim itself had problems

interpreting the data it would seem too early to be making major extrapolations to the clinical situation.

Such problems made it difficult to rank NSAIDs in the way suggested in the Vane quotation in the leaflet. COX-2:COX-1 selectivity did not show such a good relationship with improved GI side effect profile as Vane suggested. This was clear from a table published by Vane himself (1995). A further example of this inconsistency was a table in The Lancet editorial which showed COX-2:COX-1 ratios for diclofenac and naproxen of 0.7 and 0.59 respectively; a ratio of less than unity classified the agents as preferential COX-2 inhibitors yet these NSAIDs, according to the leaflet, showed intermediate risk. Searle alleged that the extrapolation was misleading in breach of Clause 7.2. Further as COX-2:COX-1 ratio data was used to imply that Mobic had some special merit, which had not been substantiated, a breach of Clause 7.8 was also alleged.

### 2 That the COX-2:COX-1 properties of Mobic conferred some special benefit to Mobic which was not shared by other NSAIDs

Searle said that the overall implication of the material was that if there was improved preferential inhibition of COX-2 then there would be an improved gastrointestinal side effect profile. This had to be defined in terms of either reduced ulcer rates in controlled endoscopic studies, or a reduction in GI complications, again in properly controlled prospective studies.

Searle was not aware of such clinical data which would support a claim for improved GI safety and Boehringer Ingelheim declined to provide such substantiation. The one published controlled study, Linden, which specifically reported GI adverse events, but did not include endoscopic assessments, reported one perforated ulcer in the Mobic 15mg group and 3 patients with GI events in the piroxicam 20mg group. The paper summary stated "Meloxicam at a dose of 15mg/per day is comparable in efficacy and safety to piroxicam 20mg". If this clinical study showed comparable safety to piroxicam, which was stated in the leaflet to show "... relatively high risk" (of GI toxicity) it was difficult to justify the whole material which was implying an improved GI safety profile for Mobic over such products as piroxicam. Linden reported one serious ulcer complication amongst 129 patients treated with meloxicam 15mg for 42 days. The incidence of complications was therefore 0.8% per six weeks. This had a confidence interval of approximately 0.04% to 3.4% and although the true complication rate was not likely to be greater than 3.4%, the study did not rule out serious complication rates up to this value over a six week treatment period. This represented an extremely high complication rate. In a study by Stead in which 261 patients received diclofenac 75mg bd for 12 weeks there was also just one serious GI complication. This was an incidence of 0.4% per 12 weeks with a confidence interval of < 0.01% to 1.7%. Thus in these two similar studies meloxicam 15mg bd was associated with twice the rate of serious GI complications in half the time relative to diclofenac 75mg bd. While the numbers of patients with complications in the studies were too small to establish the statistical significance of any excess risk to patients on meloxicam, a four fold increase in the incidence of serious complications relative to diclofenac clearly did not suggest that the risk of GI complications with meloxicam was any smaller than the risk associated with diclofenac.

Searle alleged that until it was shown that Mobic was associated with a low rate of endoscopic ulcers or a low rate of GI complications, claims for improved GI safety were unfounded, exaggerated and in breach of Clause 7.8. The material implied improved GI safety with Mobic and was therefore misleading in breach of Clause 7.2.

Searle said that identical claims were made in the journal advertisement. Breaches of Clauses 7.2 and 7.8 were similarly alleged.

Searle alleged that the "Dear Doctor" mailing did not have the generic name adjacent to the brand name and the small size of the black triangle was in breach of Clause 4.2 of the Code.

**RESPONSE**

Boehringer Ingelheim said that Mobic was licensed for use in February 1996. Boehringer Ingelheim submitted that neither the "Dear Doctor" mailing nor the journal advertisement made any direct promotional claims as to the properties of Mobic. The company accepted that there might be implied claims for Mobic insofar as the material introduced the science of COX-1 and COX-2 enzyme inhibition, their structure, properties and their possible relevance to observed clinical toxicities for the NSAIDs cited. The company's submission was as follows:-

### 1 That Mobic was in some way a novel agent in terms of its COX-2:COX-1 inhibition ratio

The company stated that Mobic was a novel agent in terms of its COX-2:COX-1 inhibition ratio. It was the first NSAID to be marketed in the UK for the licensed indication oesteoarthritis and rheumatoid arthritis for which the active principle had been shown experimentally to inhibit consistently the COX-2 enzyme in preference to the COX-1 enzyme. Boehringer Ingelheim was surprised that Searle sought to disparage the science behind the COX-1/COX-2 hypothesis based as it was on a variety of scientific and medical opinions and particularly given that Searle was already working on a selective COX-2 inhibitor. Searle had stated that its researchers had isolated compounds which were highly selective for the COX-2 enzyme and studies showed that these compounds inhibited arthritis in animals and although NSAIDs would normally lead to gut damage, no such effects had been observed. Further the company had stated that the prospect of treating arthritis without gastroduodenal complications would present a phenomenal advance. It was precisely in the direction of such advance that Boehringer Ingelheim was moving with the introduction of Mobic.

The COX-2:COX-1 inhibition ratios referred to in the material had been derived from a number of published *in vitro, ex vivo* and *in vivo* test systems which had shown consistency in their ranking of various NSAIDs with respect to COX-2:COX-1 ratios; meloxicam consistently produced a ratio reflecting inhibition of COX-2 activity at a lower concentration than that required to produce 50% inhibition of COX-1 activity ($IC_{50}$ values). The data published by Professor Engelhardt from Boehringer

Ingelheim using stimulated and non-stimulated guinea pig peritoneal macrophages to derive COX-2 and COX-1 $IC_{50}$ values respectively, had been supplemented by data derived by Churchill *et al* using COS A2 cells that were stably transfected with human COX-1 and COX-2 in whole cell assay. Both data sets showed a consistent ranking of meloxicam as the only NSAID to preferentially inhibit COX-2 as opposed to COX-1. In this system, ibuprofen, naproxen, 6-MNA (the active metabolite of nabumetone), indomethacin and aspirin selectively inhibited COX-1; while diclofenac, nimesulide and piroxicam were equipotent inhibitors of both enzymes. Meloxicam also proved to be highly selective for COX-2 in a microsome enzyme system investigated additionally by Churchill *et al*. Furthermore, Professor Sir John Vane had published independent data from which COX ratios had been derived using a further example of an experimental test system using whole cultures of stimulated J774.2 macrophages to derive a COX-2 inhibitory value and whole cultures of bovine aortic endothelial cells as a source of COX-1. The data again confirmed the preferential inhibition of COX-2 by meloxicam.

Boehringer Ingelheim submitted that when a correlation was sought between the results of epidemiological studies and these experimental COX-2:COX-1 ratios, it was evident that higher COX-2:COX-1 ratios correlated with greater gastrointestinal side effects. Meloxicam might thus be expected to product fewer adverse effects including peptic ulceration, bleeding and perforation than comparator drugs consistently associated with a higher ratio.

To illustrate the correlation between the experimental and epidemiological data, Boehringer Ingelheim referred to a composite table prepared by Vane which ranked existing NSAIDs alongside the odds ratios for bleeding and perforation (Garcia Rodriguez) or acute gastrointestinal bleeding (Langman) and the CSM rank order of adverse events of gut toxicity expressed per million prescriptions in the first 5 years of marketing. To quote Vane, "a good relationship is indeed shown between COX-2 selectivity and an improved side effect profile".

The Vane quotation was dismissed by Searle as "just one personal opinion - which is not held by many other experts in the field". This statement was not only disparaging of the eminent scientist concerned but was also incorrect and at odds with the direction of Searle's own R & D programme as well as other clinically relevant opinions noted above and as follows.

Searle quoted Clause 7.2 of the Code in relation to Mobic despite the fact that no product claims had been made. The question of "appropriate clinical studies" to "verify the case" (for COX-2 selectivity) was not appropriate. Searle furthermore stated that "even if it were unrelated to Mobic - the statement was not truly representative of all the evidence relating to the issues" and cited references in which Hallyar and Bjarnason, on full reading, in fact concurred with Vane that "the development of highly selective COX-2 inhibitors may represent a major advance in the quest for a safe NSAID" and introduced a specific discussion in relation to $IC_{50}$ ratios.

Vane pointed out that derived ratios were system specific and that "sources of variation between animal and human preparations, between recombinant enzymes and cells, and time of incubation - may influence the ratio". Thus, "when individual ratios from several systems are examined it is clear that the rank order of COX-2 selectivity is broadly similar between systems".

Although contributing the comments cited by Searle to the scientific discussion in 1995, Dr Bjarnason had in 1996 stated: "most conventional NSAIDs have a preferential affinity for COX-1. Selective COX-2 inhibitors have been developed in the hope of maintaining efficacy while improving gastrointestinal tolerability. Meloxicam has a degree of selectivity for COX-2. The preliminary data evaluating the tolerability and efficacy of meloxicam are encouraging. Much work is still to be done, but meloxicam conforms to many expectations associated with the development of more selective COX-2 inhibitors".

Searle referred to the work of Churchill *et al* but quoted selectively the comment made in relation to the profile of NSAIDs in whole cell assay systems, whereby "interpretation and comparison of the results of these studies is complicated by the different assay conditions, species and cell types that have been used". The authors of this paper went on to state that the relative order of potency of inhibitors against cyclo-oxygenase activity in a particular cell type could be determined and that the results depicted were "consistent with a previous (published) report of preferential inhibition by meloxicam of COX-2". Thus the Boehringer Ingelheim scientists experienced no problem in the interpretation of the data with respect to COX-2 inhibition.

It was incorrect to state that Vane was responsible for ranking NSAIDs in the way referred to in Boehringer Ingelheim's promotional item. Bateman published the ranking system to which Searle referred in 1994, pointing out the general agreement between the CSM derived safety data and those published by Langman *et al* and Rodriguez. Vane underlined the "good relationship between COX-2 selectivity and improved gastrointestinal side-effect profile".

The latest edition of Goodman & Gilman, The Pharmacological Basis of Therapeutics, stated that "the inhibition of COX-2 is thought to mediate, at least in part, the anti-pyretic, analgesic and anti-inflammatory actions of NSAIDs, but the simultaneous inhibition of COX-1 results in unwanted side effects, particularly those leading to gastric ulcers, that result from decreased prostaglandin and thromboxane formation".

Further support for the concept that preferential COX-2 inhibition would provide a beneficial risk benefit profile for new NSAIDs was provided by written comments from Professor J Fries, who established the ARAMIS database (comprising 17,000 patients with rheumatic disorders) and Professor Frolich.

In a review of the pharmacology, safety data and therapeutics of COX-2 inhibitors Professor Paul Emery concluded that "meloxicam's extensive clinical trial programme has demonstrated equivalent efficacy to standard NSAIDs at equipotent doses but with a lower incidence of gastrointestinal side effects. This improved risk/benefit ratio for meloxicam is likely to be due to its selectivity towards COX-2".

This summary of the experimental data with respect to

current NSAIDs and to meloxicam justified Boehringer Ingelheim's view that this drug was different from other presently available NSAIDs. Boehringer Ingelheim submitted that nothing that it had said in the items in question in any way misled, exaggerated or improperly promoted the experimental properties of Mobic.

**2 That the COX-2:COX-1 properties of Mobic conferred some special benefit to Mobic which was not shared by other NSAIDs**

Boehringer Ingelheim submitted that it had not claimed nor did it intend to claim that any clinical benefit seen during treatment with Mobic was due to its COX-2:COX-1 ratio. What it would claim was that in randomised comparative clinical trials Mobic had been shown to have a superior gastrointestinal safety profile compared to the products cited and that in keeping with the experimental and epidemiological data this might be due to preferential inhibition of the COX-2 enzyme by Mobic.

Distel *et al* recently published a pooled analysis of clinical trials which demonstrated the safety profile of meloxicam. Boehringer Ingelheim submitted that the data supported a potential claim for improved safety profile on the basis of an improved gastrointestinal (GI) side effect profile. Searle referred to an isolated study published by Linden *et al* which investigated the efficacy and tolerability of meloxicam in comparison with piroxicam in patients with an established diagnosis of osteoarthritis of the hip. One patient in the meloxicam treated group developed a duodenal ulcer (perforated) and three in the piroxicam treated group developed either bleeding/perforated gastric or duodenal ulcers. This trial was a high dose trial and did not on its own provide the basis of any claim of superiority with respect to GI safety whereas the analysis published by Distel clearly did so. The "relatively high risk" statement on the promotional leaflet related to the ranking produced by Bateman/Langman/Rodriguez for currently available NSAIDs and not to meloxicam. Furthermore, the recommended dose for meloxicam in the treatment of patients with osteoarthritis was 7.5mg. The confidence intervals calculated by Searle in relation to the Linden paper were therefore not relevant.

Searle attempted to extrapolate from its gastrointestinal unpublished data in relation to diclofenac 75mg bd in order to make predictions with respect to complication rates. Searle further asserted, incorrectly, that meloxicam was prescribed on a bd basis. Mobic was a once a day treatment. Furthermore, it stated that the complication rates of the unpublished study were too small to establish statistical significance of excess risk; yet decided to make a comparison without knowledge of Boehringer Ingelheim's database. Searle concluded that until it was shown that Mobic was associated with a low rate of endoscopic ulcers or low rate of GI complications, claims of improved GI safety were unfounded, exaggerated and in breach of Clause 7.8. It overlooked the fact that the papers cited did not state that meloxicam had an improved GI safety but introduced scientific and clinical concepts that had been recently discussed in detail in peer-reviewed journals as being of relevance to current prescription and future NSAID development.

The safety of Mobic had been demonstrated to licensing authorities around the world and would be provided in support of any claims made with respect to the safety profile of Mobic. Until such claims were made, Boehringer Ingelheim reserved the right to avoid substantiating claims that might be suggested or inferred by competitors and rejected the assertion that it was in breach of Clauses 7.2 and 7.8 of the Code.

The black triangle requirement was not part of the Code and therefore observations as to size could not be in breach of the Code. The information and only reference to Mobic was on the prescribing information which was complete and included the generic name actually adjacent to the brand name. Boehringer Ingelheim submitted that this fulfiled the requirements of Clause 4.2.

**PANEL RULING**

The Panel first considered whether or not the material at issue was promotional. The Panel noted that the "Dear Doctor" letter stated that soon a doctor would "... be able to distinguish between NSAID treatments" and it also referred to "new anti-inflammatory drugs". Prescribing information was printed on the back of the letter. The leaflet and the journal advertisement asked the question "So is there room for improvement?". Overall the Panel considered that all the material was promotional for Mobic by implication. In the Panel's view, doctors reading the material would be left with the message that Mobic was a significant improvement in treatment by inhibiting COX-2 selectively and that this resulted in an improved safety profile compared to other NSAIDs.

The Panel accepted that it had been established that NSAIDs had different COX-2:COX-1 inhibition ratios and that there was some evidence that the difference in the levels of gastrointestinal side effects correlated with this ratio. There was however insufficient evidence on the use of highly selective COX-2 inhibitors to establish that this theoretical concept translated into definite clinical benefit.

The Panel noted from its submission that Boehringer Ingelheim would claim that in randomised comparative clinical trials Mobic had been shown to have a superior gastrointestinal safety profile compared with the products cited and that in keeping with the experimental and epidemiological data this might be due to preferential inhibition of the COX-2 enzyme. However the material at issue by implication claimed more than this by suggesting that the COX-2 concept was proven and responsible for improved safety. As all the claims were by implication and there was no qualification, it was likely that at least some doctors would gain the impression that rather than being associated with a reduced incidence of gastrointestinal side effects, Mobic was associated with none. This was clearly misleading as data by Distel *et al* showed an incidence of GI side effects of approximately 17% with Mobic. This was significantly less than with other agents but was still far from negligible. The Panel noted that the summary of product characteristics of Mobic stated that as with all NSAIDs long term administration had been associated with an increased risk of gastrointestinal side effects.

The Panel considered that overall the material was misleading and therefore ruled a breach of Clause 7.2 of the Code. Further the Panel considered that the claims were exaggerated and implied a special merit for Mobic

which could not be substantiated. A breach of Clause 7.8 was ruled.

The Panel noted that the size of the black triangle was not a requirement of the Code. The Code provided guidance about the size of the black triangle in the supplementary information to Clause 4.2 of the Code. The Panel requested that Boehringer Ingelheim's attention be drawn to this supplementary information. The Panel noted that the non-proprietary name appeared immediately adjacent to the most prominent display of the brand name which was given as the heading to the prescribing information. The Panel therefore ruled no breach of Clause 4.1 of the Code.

## APPEAL BY BOEHRINGER INGELHEIM

Boehringer Ingelheim submitted that the mailing and the journal advertisement were sent out in order to alert doctors to the imminent launch of Mobic. Both items were intended to inform doctors that not only was there evolving science in the pharmacology of new treatments for rheumatic diseases but also there was evidence of a rank order with respect to pharmacological effects and observed clinical effects and that there was a correlation between the two. None of this information involved Mobic and therefore at most there could only be an implied relationship between Mobic and the relative COX-1 or COX-2 enzymatic inhibition on the one hand and implied relationship between the clinical NSAID safety record derived from epidemiological data arising in the UK and the clinical (gastrointestinal) safety profile of Mobic on the other hand.

Despite the absence of claims for meloxicam by Boehringer Ingelheim, Searle suggested claims from the material which, indeed, was promotional for Mobic but did not specify what those claims would be. Boehringer Ingelheim submitted it was important to spell out to doctors that the science was evolving, that the science was deemed to be of clinical importance and that a new product with relevant attributes with respect to pharmacological effect and clinical safety was shortly to be launched.

Boehringer Ingelheim submitted that it had presented data, Distel *et al*, to the Panel which clearly showed statistically significantly lower rates of reported GI adverse events for Mobic than comparator NSAIDs thereby supporting claims of improved GI safety. Further unpublished evidence was provided by the results of a study, the MELISSA study which compared 7.5mg Mobic with 100mg slow release diclofenac and showed it to be significantly better tolerated. The Panel did not appear to have ruled on this specific allegation.

The allegation that the promotion implied improved GI safety with Mobic appeared to be that part of the complaint that the Panel had ruled on. The Panel had considered that "Doctors reading the material would be left with the message that Mobic was a significant improvement in treatment by inhibiting COX-2 selectivity and this resulted in an improved safety profile compared to other NSAIDs". Boehringer Ingelheim pointed out that the material stated "However, none of the drugs mentioned above has been shown to inhibit COX-2 preferentially". The reasonable implication of this statement was that Mobic did inhibit COX-2 preferentially. There was good evidence that this was so but it was not appropriate to imply selectivity for Mobic as there was no such suggestion. Secondly, nowhere in the material was there any statement that preferential or selective COX-2 inhibition led to better gastrointestinal tolerance. There was a clear correlation between the two but no claim of a causal relationship. Nowhere in the material was there a statement that suggested "that the COX-2 concept was proven and responsible for improved safety" as the Panel stated was implied. Indeed the statement made was that "Recent evidence suggests that ... the undesirable effects occur through inhibition of COX-1".

Boehringer Ingelheim submitted that the Panel's conclusion that "There was, however, insufficient evidence on the use of highly selective COX-2 inhibitors to establish that this theoretical concept translated into definite clinical benefit" was based only on limited information available to the Panel. The company provided a detailed review of the topic which clearly demonstrated that the COX-2:COX-1 assessments and their correlation with clinical experience.

Boehringer Ingelheim submitted that it was difficult to see how the Panel could conclude that "it was likely that at least some doctors would gain the impression that rather than being associated with a reduced incidence of gastrointestinal side effects, Mobic was associated with none." The COX-2:COX-1 ratio for Mobic was not described in the material so the only reasonable conclusion possible was that it had a more favourable ratio than existing NSAIDs. Furthermore there were no clinical data provided on Mobic so the only reasonable conclusion possible was that the ratio would be more favourable than existing NSAIDs.

Finally the material clearly stated that Mobic was not available and therefore could not be prescribed. This and the rhetorical question "So is there room for improvement?" implied that further information would be forthcoming to provide clear statements as to the COX-2:COX-1 ratio for Mobic and to its clinical data on efficacy and gastrointestinal tolerance. This introductory material had now been superseded by promotional material that addressed the question "So, is there room for improvement?".

Boehringer Ingelheim considered that the pre-clinical, *in vitro, in vivo* and clinical data available justified rejection of the two main breaches of the Code alleged by Searle in that they showed the clinical relevance of experimental data and improved gastrointestinal safety of Mobic.

## APPEAL BOARD RULING

The Appeal Board noted that the beginning of the "Dear Doctor" letter which accompanied the mailing stated that:

"Soon you will be able to distinguish between NSAID treatments in a way previously unknown.

As you know, NSAIDs work by inhibiting the action of the enzyme cyclo-oxygenase (COX). But, as you will see from the enclosed information, this is not the full story.

The good news is that with new anti-inflammatory drugs, you may be able to inhibit physiological and

inflammatory processes differentially. This is because COX has now been found to exist in two distinct forms. COX-1 has a valuable physiological function such as in the gut, while COX-2 is induced in inflamed joints."

Both the mailing and the journal advertisement discussed COX-1 and COX-2 and ended with a quotation from Vane that "... a good relationship is indeed shown between COX-2 selectivity and an improved gastrointestinal side-effect profile ..." followed by "However, none of the drugs mentioned above has been shown to inhibit COX-2 preferentially. So, is there room for improvement?" Mobic was not mentioned by name in the text but was mentioned in the prescribing information on the items. The Appeal Board considered that readers would conclude that Mobic was associated with the features highlighted in the material. The Appeal Board considered that doctors would be left with the message that Mobic was a significant improvement in treatment by inhibiting COX-2 preferentially and that this resulted in an improved safety profile compared to other NSAIDs.

The Appeal Board considered that the company did not have clinical data to support the implied claims. The Appeal Board therefore agreed with the Panel that overall the material was misleading and that the claims were exaggerated and implied a special merit for Mobic which could not be substantiated. The Appeal Board upheld the Panel's rulings of breaches of Clauses 7.2 and 7.8 of the Code.

The appeal therefore failed.

**Complaint received** 15 August 1996

**Case completed** 29 November 1996

---

**CASE AUTH/463/9/96**

# SERONO v ORGANON

## "Orgyn" magazine

**Serono complained about "Orgyn", a magazine on women and health issued by Organon.**

**The Panel considered that the magazine was a promotional item for Organon's product Puregon. Some claims for the product were ruled to be acceptable in that hanging comparatives had not been used as alleged but the claim of "unique convenience" was considered to be unjustified and ruled in breach of the Code.**

**The brand name of another company's product was included in a reference to a published study. Although the Code stated that clear references must be given this did not extend to the use of other companies' brand names and these needed to be edited out. A breach of the Code was ruled. Another breach was ruled in that the prescribing information was incomplete.**

Serono Laboratories (UK) Ltd complained about a magazine on women and health, "Orgyn" issued by Organon Laboratories Limited. The 56 page, A4, glossy magazine was subtitled "Puregon Special Issue".

### COMPLAINT

Serono said that it had recently received a mailing from Organon, despatched in the UK, entitled "Orgyn". The mailing, which took the form of a magazine, contained three main advertisements for Puregon, appearing on the inside front page, inside back page and on pages 42-43. The piece clearly constituted an advertisement for Puregon. Serono made a number of complaints about the articles.

Serono alleged a breach of Clause 7.2. Organon had used the hanging comparisons "greater efficacy" and "more efficient" and had claimed "lower total doses" and "shorter treatment times" but did not identify the comparator.

Serono alleged a breach of Clause 7.8. The term "unique" could not be substantiated.

Serono alleged a breach of Clause 7.10 as a reference was made to the Serono brand name Metrodin without the company's permission.

Serono alleged that there was a contravention of the European advertising regulations (Council Directive 92/28/EEC, Chapter III Article 6) as the supply classification of the medicinal product was not included.

### RESPONSE

#### Clause 7.2 - Use of hanging comparisons

Organon said that the phrases "greater efficacy", "more efficient", "lower total doses" and "shorter treatment times" were not, as claimed by Serono, hanging comparisons as in each case the text qualified the claims by stating "... as compared to urinary FSH". Furthermore, the statements were supported not only by the references given on the pages concerned, but also by the summary of product characteristics (SPC) for Puregon which stated: "In these studies it was shown that Puregon is more effective than urinary FSH in terms of a lower total dose and a shorter treatment period needed to achieve pre-ovulatory conditions. Therefore, it may be appropriate to give a lower dosage of Puregon than for urinary FSH".

#### Clause 7.8 - Use of the term "unique"

Organon said that follitropin-beta was a complex molecule which was a product of recombinant technology. It had a specific INN [international non-proprietary name] which signified that it was recognised as being a unique molecule and was slightly different in structure to both urinary-derived human FSH and follitropin-alpha. Furthermore, in contrast to the statement quoted above on the efficacy of Puregon (follitropin-beta), the SPC for follitropin-alpha (Gonal-F,

Serono) revealed that it was not equivalent to urinary FSH. The use of the term "unique convenience" was further justified by the fact the Puregon was the only FSH to be available in a lyosphere presentation. This formulation was totally unique and permitted maximum solubilisation of the product, thereby maximising the bioavailability to the patient.

### Clause 7.10 - Use of the brand name Metrodin

Organon said that the brand-name Metrodin was only used within the terms of the reference by Out HJ *et al.* The use of brand-names within a referencing system was permitted and Clause 7.5 of the Code stated that "When promotional material refers to published studies, clear references must be given".

### Price and supply classification

Organon accepted that the item in question should have included both the legal category of Puregon and the UK price. Organon apologised for this omission and would endeavour to ensure that such an oversight did not occur again.

Organon said that it had halted the use of the magazine and had recalled it as far as was possible. It was distributed both via a mailing list to consultants and GPs with a gynaecological interest and to family planning clinics.

### RULING

The Panel considered that the item in question constituted promotional material for Puregon subject to the Code. It was "Organon's magazine on women and health", entitled "Orgyn" and subtitled "Puregon special issue". The format of the item was unusual. It had the general appearance of a medical journal. The front cover highlighted some of the articles contained inside and page 1 listed the contents. The Panel noted that some of the articles were directly related to Puregon while some of them were of a more general nature, such as an article describing the "mother & child" theme in modern art. The inside front cover, pages 42-43 and the inside back cover carried overtly promotional material for Puregon. These pages had the appearance of, and would almost certainly be taken by readers to be, journal advertisements. The Panel did not, however, consider that the item was a journal in the accepted sense of the word. It was company produced material concentrating on Puregon. The Panel considered that "Orgyn" was a 56 page promotional item for Puregon and this was the basis on which it made its rulings.

The Panel noted that the letter of complaint referred at first to the inside front cover, the inside back cover and pages 42-43 within the mailing but went on to refer to the articles. Noting the context, the Panel considered that by "the articles" Serono was in fact referring to these four pages and this was the basis on which the case was considered. It was not for the Panel to search through a 56 page item to see if the words or phrases complained of appeared anywhere else. The Panel also noted that Serono referred to EC requirements. It was not within the jurisdiction of the Panel to judge compliance with such requirements but the Code itself covered them. The Panel's role was to make rulings under the Code of Practice.

The Panel noted that the first claim on the inside front cover was was "Puregon .... offering greater efficacy .... as compared to urinary FSH". The text went on to mention more efficient induction, lower doses and shorter treatment times. The Panel considered that the first part of the claim had clearly stated the comparator and so "greater efficacy" could not be viewed as a hanging comparison. The efficacy of Puregon was clearly being compared with that of urinary FSH. In the circumstances, the Panel did not consider it necessary to note the comparator in every sentence once the claims had been put into context and so the statements regarding induction, dosing and treatment times were similarly not regarded by the Panel as hanging comparisons. No breach of Clause 7.2 of the Code was ruled.

The Panel noted that the inside front cover carried the claim "Puregon .... offering .... unique convenience ....". The Panel noted that the supplementary information to Clause 7.8 of the Code stated that great care needed to be taken with the use of the word "unique". If the word was to be used at all, it should be used to describe some clearly defined special feature of a medicine and not be used to simply imply a general superiority. In the Panel's view every product could be described as unique in its own way but this would not justify the use of the word in advertising. Although the Puregon SPC referred to studies showing effectiveness at a lower dose and shorter treatment period then urinary FSH, it was cautious on the matter and said that "It may be appropriate to give a lower dose" than of urinary FSH. The Panel considered that the use of the term "unique convenience" in relation to Puregon was an unjustified claim for superiority and a breach of Clause 7.8 was ruled.

The Panel noted that the claims on the inside front cover and on pages 42-43, were referenced to a study. Organon had given the full reference for the study including the title which included the name of Serono's product Metrodin. The Panel noted the requirements of Clause 7.5 of the Code which stated that where promotional material referred to published studies, clear references must be given. Clause 7.10 of the Code, however, stated that the brand names of other companies' products must not be used unless the prior consent of the proprietors had been obtained. Clause 7.5 did not mean that Clause 7.10 could be ignored in relevant circumstances. Other companies' brand names needed to be edited out of references given in promotional material. A breach of Clause 7.10 was ruled.

The inside back cover of the item contained a section of text headed "Basic Succinct Statement". The information given under the heading was broadly that set out in Clause 4.2 of the Code but it lacked a number of features, such as the product licence number, the legal category of the medicine and its price. Full prescribing information should have appeared in the publication and a breach of Clause 4.1 of the Code was ruled. As the item was more than four pages in length, there should have been a statement as to where the prescribing information could be found, in accordance with Clause 4.6.

| | |
|---|---|
| **Complaint received** | **9 September 1996** |
| **Case completed** | **6 November 1996** |

CASE AUTH/466/10/96

# UNIVERSITY DOCTOR v BOEHRINGER INGELHEIM

## Mobic hospital detail aid

**A university doctor complained about a hospital detail aid for Mobic issued by Boehringer Ingelheim. One page of the detail aid featured an editorial, jointly published by the complainant and another doctor, and highlighted a quote from it. The complainant alleged that the quote had been used out of context and implied his support for Mobic despite the fact that he and his co-author were openly critical about claims being made for its gastrointestinal safety.**

**The Panel noted that the editorial was a general review and did not refer to any medicine. The quote, which referred to selective COX-2 inhibition and gastrointestinal tolerability, had been taken from a passage describing the current direction of pharmaceutical research. The Panel considered, however, that as the quote was opposite a page referring to preferential COX-2 inhibition and Mobic it would be taken to support the gastrointestinal tolerability of the product. The Panel considered that the views of the authors had been misinterpreted and in that sense the detail aid was misleading. Breaches of the Code were ruled.**

A senior lecturer and honorary consultant complained about the promotion of Mobic (meloxicam) by Boehringer Ingelheim Limited. The material in question was a hospital detail aid which took the form of loose leaf A4 sheets in a ring binder. A number of pages of the detail aid featured a faint copy of a scientific paper each of which was prominently overlaid with a coloured box containing a quote from the paper. The page at issue featured an editorial from The Lancet, written by the complainant and another doctor. The highlighted quote from the paper was "Selective COX-2 inhibition has become a target for treatment, based on the promise of gastrointestinal tolerability". Immediately adjacent to the coloured box was written the name of one of the authors together with the year of publication, 1995.

### COMPLAINT

The complainant said that he had very substantial concerns about the marketing of meloxicam (Mobic) by Boehringer Ingelheim. Together with another doctor, he had written an editorial in The Lancet which highlighted the development and emergence of highly specific inhibitors of cyclooxygenase-2 (COX-2) and their possible gastrointestinal safety. In subsequent correspondence some aspects of this editorial were supported but there was also some criticism which appeared to be written principally to promote meloxicam. This was not by itself of any concern but the complainant and the other doctor had pointed out in another letter to The Lancet that meloxicam did not fulfil the criteria of a highly specific inhibitor and that if anything it was marginally safer than piroxicam which headed most toxicity NSAID ranking lists.

Meloxicam had now been launched and the advertising style seemed to the complainant to be unacceptable as it made no distinction between highly selective inhibition of COX-2 and preferential selectivity. The advertising material consistently implied gastrointestinal safety, but there was simply no, or unacceptable, data available to support these implications. Indeed the complainant was so concerned at the possible consequences of this advertising that he had sent a letter to The Lancet which awaited publication. The medicine simply did not live up to the advertising hype and the uninitiated user, who had not got insight into the mechanism of NSAID toxicity to the gastrointestinal tract, might be led into false security and place his/her patient at serious risk on meloxicam with potential devastating consequences.

The complainant said that it had now been drawn to his attention that representatives of Boehringer Ingelheim were using a detail aid to promote the drug using a photostat of the editorial that he and his co-author had written, highlighting in bold the other doctor's name and providing a selective quotation from the editorial. This clearly implied support for the product. However, neither author had been asked permission from the company to quote from their editorial. More importantly, Clause 11.2 of the Code stated that "Quotations from medical and scientific literature, or from personal communications must accurately reflect the meaning of the author". The complainant's and the other doctor's Lancet letter clearly distinguished between preferential (which was associated with damage) and highly specific inhibition of COX-2 (which was proposed not to cause damage). They had gone out of their way to point out the possible toxicity of meloxicam but inclusion of the editorial in promotional copy would seem to imply that they somehow endorsed Boehringer Ingelheim's claims of gastrointestinal safety, which could not be further from the truth.

Clause 11.4 of the Code stated "The uttermost care must be taken to avoid ascribing claims or views to authors when these no longer represent the current views of the authors concerned". The Lancet letter fully described the complainant's and the other doctor's feeling about the medicine along with the numerous correspondence that the complainant had had with Boehringer Ingelheim's central German office. Again the quote would seem to imply their acceptance or support of Boehringer's claims.

The complainant said that Boehringer Ingelheim had used his and his co-author's material and names in bold in the detail aid without permission and out of context. The complainant was totally incensed by this behaviour which was clearly going to dent his and the other doctor's reputations and scientific standing. It implied support for the product at a time when if anything they were warning against the danger of the safety claims.

In addition to Clauses 11.2 and 11.4, referred to by the complainant, the Panel asked Boehringer Ingelheim to consider Clauses 2, 7.2 and 9.1 of the Code.

### RESPONSE

Boehringer Ingelheim submitted that the complaint apparently related to a single page of the hospital detail

aid, to which the complainant objected insofar as a quotation from an editorial had been highlighted by Boehringer Ingelheim together with the name of the complainant's co-author. The editorial referred to "selective COX-2 inhibition" and "the promise of gastrointestinal tolerability". The complainant made no reference to preferential COX-2 inhibition nor to meloxicam in particular. The page in question in the detail aid was juxtaposed to a page containing information regarding *in vitro* experiments providing information on the comparative properties of meloxicam and other agents.

It was clear to the company that the complainant had been shown the page complained of by a third party since no sales representative of Boehringer Ingelheim had called on him before or after the launch of Mobic. If the complainant had not seen the entire detail aid then one must conclude that he had not been able to discern the background in which Mobic had been developed and thus that he was unaware of the context to which his editorial was deemed to refer.

The page in question was one of 22 in the hospital detail aid - designed for consultant physicians, primarily rheumatologists. Of these, eight pages showed a quotation from a scientific article or editorial written by an authority in the field. All were published. The theme encompassed by these pages was that of the evolving knowledge and developing science regarding the relevance of COX-2 inhibition as well as the consistency of opinion in this field. One page referred to the economic burden of NSAID toxicity. Thus the context was one of evolving science in an important and costly therapeutic field. Within that context Mobic was offered as an advance upon existing treatment. The advance was that of preferential pharmacological inhibition of COX-2 relative to COX-1 on the one hand and an improved safety profile in comparative terms on the other. There was an implied relationship between the two but not an established one. The quotation pages were fully referenced and review of all of these articles showed that the authors did not have meloxicam specifically in mind. Although the company respected the complainant's right to object to the use of his editorial in whole or in part, the quote supported the science, was in the public domain and reflected his present opinion. Boehringer Ingelheim did not believe such use, given the context as described above, constituted either misrepresentation of the meaning of the author(s), nor that views had been ascribed to the author(s) when he (they) did not hold those views.

Boehringer Ingelheim was aware of and had read carefully the correspondence following the complainant's editorial to which he referred and were conscious of the comments regarding meloxicam in his and his co-author's response to the letters that followed the editorial. The complainant had also commented as an independent reviewer of the meloxicam New Drug Profile published subsequently in "Drugs". In the company's opinion the correspondence following his letter to The Lancet had not altered the opinion expressed in his editorial. Further, Boehringer Ingelheim believed that his opinion of meloxicam as expressed in 1995 was influenced by the data to which he was given access subsequently by Boehringer Ingelheim and for his review in Drugs 1996.

Firstly as to the editorial, the quotation was accurate, reflected the authors' views, related to COX-2 selectivity and made no reference to meloxicam. Given the context of all the "quotation" pages and the evolving science and knowledge, the quotation from the complainant and his co-author was not only relevant but in common with the other "quotation" pieces. The authors neither endorsed nor specifically promoted Mobic. The complainant declared that his opinion of meloxicam differed from his opinion expressed in The Lancet editorial and that Boehringer Ingelheim had ignored that. On the contrary Boehringer Ingelheim had followed carefully the letters to The Lancet to which the complainant referred including that in which he was critical of the data supporting meloxicam. Correspondence between the complainant and Boehringer Ingelheim's pharmacology department subsequent to his Lancet letter showed that he had retracted his opinion. Boehringer Ingelheim had adequate reasons to believe his opinion of its product had changed and thus the company was not in breach of Clause 11.4 nor Clause 11.2.

With regard to Clause 7.2, Boehringer Ingelheim questioned whether the use of the editorial misled directly or by implication. The editorial was fully referenced and reading of it suggested a probable therapeutic value in having COX-2 selective NSAIDs. Preferential inhibition of COX-2 by meloxicam which was not mentioned in the editorial would appear to be an advance in the direction of COX-2 selectivity. The editorial neither explicitly nor implicitly endorsed meloxicam and therefore use of the editorial within the context specified in the detail aid for Mobic really could not mislead as to the product or the authors' view.

In considering Clause 9.1 Boehringer Ingelheim said that clearly a healthcare professional might take offence at what he or she saw or understood. The question then became, was it reasonable for that person to take offence and was the material intrinsically offensive? High standards of science were being referred to as the context of the detail aid and the material did not depart from the requirement that the specific nature of medicines and the professional standing of the recipient of the material be respected.

The whole detail aid was constructed in a professional way aiming to highlight the science and the current advances in drug development that were occurring and the fact that meloxicam had attributes, both pharmacological and clinical, that merited the medicine being placed in such a context as a "step along the path".

Boehringer Ingelheim regretted the complainant's displeasure but could not concede that this constituted a breach of Clause 9.1.

Boehringer Ingelheim submitted that it was hard to see how Clause 2 could be invoked here. Was it because the complainant was annoyed, because he had written a letter of complaint to The Lancet or because Boehringer had not sought his permission to quote his current opinion? It was certainly not a Code of Practice requirement to ask permission from the authors to quote from literature in the public domain. Nor was the item quoted out of context. The context was the evolution in knowledge and understanding of NSAID mechanisms of action reported within the last five years, about which there was still some debate and further investigation to be performed. It was

not yet clear that COX-2 selective inhibition was proven devoid of gastrointestinal toxicity.

Turning to the general tone of the complainant's letter, Boehringer Ingelheim said that it appeared to be his opinion that its advertising material consistently implied gastrointestinal safety. This was simply not so any more than the assertion that the company did not differentiate between COX-2 selectivity and COX-2 preferential inhibition. The former would only imply hypothetical gastrointestinal safety while the latter implied or may be associated with decreased frequency of gastrointestinal side effects. Clearly preferential inhibition of COX-2 did not imply **NO** inhibition of COX-1.

Boehringer Ingelheim could not accept that the product did not live up to what the complainant called the "advertising hype" if by that expression he meant a claim for improved safety. The paper by Distel *et al* (a global safety analysis of data from meloxicam clinical studies) and the results of a recently reported trial confirmed the claim. At the doses tested meloxicam was superior in terms of overall gastrointestinal adverse effects compared to diclofenac 100mg SR, piroxicam 20mg, naproxen 750-1000mg ($p<0.05$). Meloxicam did not show advantage over diclofenac 100mg SR in terms of serious adverse gastrointestinal events but was superior to piroxicam and naproxen ($p<0.05$). The recently reported trial confirmed, or was consistent on a very large scale with, the Distel analysis of the pooled randomised clinical trial data with respect to meloxicam and diclofenac SR. These data showed significantly fewer overall gastrointestinal side effects with meloxicam. The occurrence of serious gastrointestinal events (upper gastrointestinal perforation, ulceration or bleeding) was not different for the two agents.

## RULING

The Panel noted that the editorial by the complainant and his co-author had been published in The Lancet and that the Code did not require companies to obtain authors' permission before using quotes from published papers. The editorial explained the theory of COX-1/COX-2 inhibition and its involvement in the pathophysiology of NSAID-related gastrointestinal side effects. The editorial was a general overview of the situation and did not refer specifically to Mobic or endorse any medicine. A table included in the editorial ranked various NSAIDs according to their relative selectivity of COX-1 and COX-2 inhibition. Two of the medicines included in this table were only referred to by numbers and could not be identified by the Panel. The authors questioned whether ranking NSAIDs in this way was the best means of predicting their propensity to cause gastrointestinal side-effects. The example was given of piroxicam and naproxen which had COX-2/COX-1 ratios of 600 and 0.59 respectively. From the theory about COX-1 and COX-2 major differences in the incidence of gastrointestinal side effects between naproxen and piroxicam might be expected. The authors stated that piroxicam generally did cause more upper gastrointestinal complications than naproxen but the difference fell far short of three orders of magnitude - indeed the similarities in rates of gastrointestinal complications were as striking as the differences in ratio of COX-1 and COX-2 inhibitory action. The relative risk (odds ratio) of serious upper gastrointestinal complications was 6.4 - 19.1 for piroxicam and 3.1 - 9.1 for naproxen. The authors said that increasing the selectivity of COX-2 might produce a more favourable outcome. The Panel noted that the editorial contained the quote "Selective COX-2 inhibition has become a target for treatment based on the promise of gastrointestinal tolerability".

A subsequent letter by the complainant and his co-author, also published in The Lancet endorsed the view that COX-2/COX-1 inhibition alone did not account for the mechanism of NSAID related damage. Particular physiochemical qualities of COX-2 selective inhibitors were also important. The authors also said that most researchers seemed to regard the mechanism of NSAID toxicity as a multipathogen process, of which COX-1 inhibition was only one important element. The last paragraph of the letter was critical of meloxicam. In one study it had seemed to be associated with gastrointestinal side effects in 28% of patients taking it for up to eighteen months.

The Panel noted that the detail aid in question was prepared in July 1996. The Panel considered that at this time Boehringer Ingelheim would have been well aware of the complainant's negative opinion of Mobic as expressed in his letter published in The Lancet seven months earlier. The quote which had been featured in the detail aid was a general statement describing the current direction of pharmaceutical research but would be seen as supporting a specific point, namely the gastrointestinal tolerability of Mobic. The Panel noted that the editorial was featured opposite a page which compared various NSAIDs according to their *in vitro* COX-2/COX-1 inhibition ratios. The Panel noted, however, that the editorial had specifically criticised this parameter as being an unreliable indicator of gastrointestinal tolerability.

The Panel considered that readers seeing a quote about selective COX-2 inhibition and gastrointestinal tolerability opposite a page detailing Mobic would inevitably link all three together. The Panel accepted that the quote was accurate, and so ruled no breach of Clause 11.2 of the Code, but noted that the authors had not written it in relation to Mobic. The authors were known to be critical of the gastrointestinal tolerability of the medicine. The Panel considered that such a general quotation should not have been used to support a specific product. The Panel considered that the quote had been used out of context and that the views of the authors had been misrepresented. Breaches of Clauses 7.2 and 11.4 of the Code were ruled. The Panel did not consider that Clauses 2 and 9.1 of the Code had been breached.

**Complaint received** **4 October 1996**

**Case completed** **27 November 1996**

CASE AUTH/468/10/96

# SMITHKLINE BEECHAM v PASTEUR MÉRIEUX MSD

## Promotion of Avaxim

**SmithKline Beecham complained that Pasteur Mérieux MSD's representatives were claiming that Avaxim, Pasteur Mérieux MSD's hepatitis A vaccine, could be used as the booster dose in patients who had initially received Havrix, SmithKline Beecham's hepatitis A vaccine, and that this was an unauthorised use. SmithKline Beecham referred in particular to material used at an Avaxim training meeting which had raised this issue and had also derided SmithKline Beecham.**

**The Panel accepted that Pasteur Mérieux MSD representatives had claimed that Avaxim could be used as a booster dose in patients who had received Havrix and ruled this to be in breach of the Code. A breach was also ruled in relation to disparaging comments made about SmithKline Beecham.**

### COMPLAINT

SmithKline Beecham Pharmaceuticals UK complained that Avaxim was being promoted by the representatives of Pasteur Mérieux MSD Ltd outside the product licence, in breach of Clause 3.2 of the Code, by claiming that Avaxim could be used to boost subjects who received an initial dose of the SmithKline Beecham vaccine, Havrix. This was first brought to SmithKline Beecham's attention following receipt of a letter sent to a practice.

SmithKline Beecham reported this to Pasteur Mérieux MSD on 19 June and received a letter claiming that, as the summary of product characteristics (SPC) did not state that Avaxim could not be used to boost Havrix, Pasteur Mérieux MSD was promoting within its licence. This was in spite of the fact that the Avaxim patient information sheet clearly stated that (if the subject) "had a primary injection of a hepatitis A vaccine other than Avaxim. If this is your first booster you should have the same product". Pasteur Mérieux MSD subsequently agreed that this claim was outside the marketing authorization and agreed to stop this from happening on 18 July 1996.

Despite this assurance, SmithKline Beecham continued to receive numerous reports that there had been no change to the promotional claims being made by Pasteur Mérieux MSD, except to back up the claim with a promise that "clinical data will soon be available", in breach of Clause 7.3. SmithKline Beecham once again wrote to Pasteur Mérieux MSD in an attempt to resolve the issue on 16 August 1996 and again received an undertaking that this practice would be stopped.

Yet again, however, reports of representatives making the claim continued to arrive regularly and a further letter was sent to Pasteur Mérieux MSD on 19 September 1996 detailing two of the representatives concerned and the area where the claim was made. Pasteur Mérieux MSD said that steps had already been taken to stop the claim being made but that it would be re-emphasised at a sales meeting. It appeared that despite Pasteur Mérieux MSD's "reassurances" to the contrary, its representatives were actively seeking to gain commercial advantage by disregarding the Code.

Whilst it could be argued that the representatives were ignoring the instructions of the company, it certainly did not appear that Pasteur Mérieux MSD had taken every action to ensure that its representatives stopped this activity. Regardless of this, Pasteur Mérieux MSD was responsible for its representatives' actions.

Indeed, review of the transcript from an Avaxim training meeting for Pasteur Mérieux MSD representatives and staff suggested that the representatives' attitude to the Code might simply reflect the attitude of senior management at Pasteur Mérieux MSD. The transcript related to a mock court scene at which the medical director of Pasteur Mérieux MSD was the "Judge". During the "trial", the medical director made comments on the debate and corrected issues that were unacceptable. As briefing material it fell under the Code, Clause 15.9.

During the "trial" SmithKline Beecham was continually derided. "Just like SB to use a trial that is not a fair representation of the data...", "have you no ethics?" and "You may offer big glossy items which look the part...." were said in relation to SmithKline Beecham. Breaches of Clauses 8.1 and 15.9 were alleged.

The transcript covered the use of Avaxim to boost subjects who had previously received Havrix and made clear that Avaxim and Havrix could be used interchangeably. The medical director did not comment on this but, rather than informing the audience and representatives that they could not make this claim, the point was re-emphasised.

SmithKline Beecham had attempted to deal with this matter without recourse to the Code. It had given Pasteur Mérieux MSD every opportunity to stop its representatives from continuing to make these false claims. It was apparent, however, that, for whatever reason, any attempts that had been made had been unsuccessful. By continuing to promote outside the product licence, despite having made a commitment to cease its activity, Pasteur Mérieux MSD had failed to maintain a high standard, breaching Clause 9.1. By continuing to seek competitive advantage, whilst accepting that it had no clinical evidence to support its claims, and by failing to make every effort to stop activity which it had previously admitted was outside the terms of its product licence, Pasteur Mérieux MSD was bringing the industry as a whole into disrepute, in breach of Clause 2. Further, the nature of the company's briefing material was such that it was likely to encourage its representatives to undertake activities that would be in breach of the Code.

Recognising the difficulty that could occur in validating claims from representatives, SmithKline Beecham was seeking permission from practices which had received such information to pass their names to the Authority and would forward these as soon as possible.

A further letter was subsequently received from SmithKline Beecham giving the names of three practices

which would be willing to discuss this matter in confidence with the Authority.

## RESPONSE

Pasteur Mérieux MSD Ltd said that the first part of the complaint seemed to be based on a letter sent out from its medical information department which SmithKline Beecham mistakenly believed to be an unsolicited mailing. This letter was written on 7 June in response to a direct enquiry made by a specific practice to one of Pasteur Mérieux MSD's representatives. The representative wanted there to be no misunderstanding on the question raised and correctly referred the issue to the medical department. Pasteur Mérieux MSD conceded that, in this instance, the letter was not specifically addressed with the individual enquirer's name which was omitted. As this letter was a response to a specific enquiry from a customer, Pasteur Mérieux MSD considered it to be exempt from the Code as set out in Clause 1.2.

When Pasteur Mérieux MSD received the complaint from SmithKline Beecham dated 19 June, it reviewed the contents of the above mentioned letter which had been sent out to the practice concerned following its enquiry. Pasteur Mérieux MSD submitted that it was relevant to point out that, by 19 June, Avaxim had only been on the market for a short time and it had been impossible to foresee the incredible demand for information and general interest that was being generated by the medical profession about the product. This meant that Pasteur Mérieux MSD's representatives and medical department were completely inundated with all types of questions on hepatitis A at this time. Similar letters had accordingly been sent out to other health professionals in response to the same enquiry. Because of Pasteur Mérieux MSD's concerns that SmithKline Beecham had misinterpreted the letter as disguised promotion, a decision was taken that this letter would not be used again. SmithKline Beecham was so advised on 25 June.

The next issue raised in the letter of complaint related to the information stated in the patient information leaflet (PIL). It was true that the PIL did not accurately reflect the SPC for Avaxim. Pasteur Mérieux MSD had already taken the necessary steps to alter the PIL. However, the contents of the PIL were not governed by the Code and were outside the allegations made by SmithKline Beecham.

Pasteur Mérieux MSD then received a further letter from SmithKline Beecham dated 1 July claiming that its representatives were advising that Avaxim could be used as a booster dose following a priming dose with Havrix Monodose. Pasteur Mérieux MSD took steps, therefore, to remind all members of the salesforce that they must not promote Avaxim outside the product licence. An e-mail was sent out by the head of medical information to the whole salesforce which was reiterated by the national sales manager.

A second e-mail was sent to reinforce the instructions that interchangeability of hepatitis A vaccines was not included in the product licence and that, although currently there were no data, clinical trials were in progress. If the representatives were pressed for more information, the appropriate response was outlined and they were told that further enquiries should be directed to the medical department.

In order to further endorse the position, all the regional sales managers were instructed at sales and marketing meetings in August and September to ensure that the salesforce continued to adhere to these instructions. Pasteur Mérieux MSD believed it took all possible measures to clarify the situation with its representatives and to emphasise all the implications.

There were situations, however, where health professionals might pose the question: "is it possible to boost patients with Avaxim following priming with Havrix?". In such circumstances, it was clear from Clause 1.2 of the Code that companies were permitted to provide information in response to specific questions. As explained above, Pasteur Mérieux MSD had provided clear guidelines to its salesforce as to the appropriate responses in such circumstances. This was obviously not promotion of Avaxim outside the product licence, but a response to a direct request for information and, therefore, was not in breach of Clause 3.2.

Pasteur Mérieux MSD received a further letter from SmithKline Beecham dated 16 August which advised that two Pasteur Mérieux MSD representatives had sent out unofficial letters which were without the knowledge or approval of the company. The representatives involved were disciplined.

With respect to the allegations made by SmithKline Beecham concerning two other named representatives, these were vague and not substantiated and, as such, were extremely difficult to pursue. As explained above, Pasteur Mérieux MSD had responded promptly to the original complaints and allegations made by SmithKline Beecham in June and July. This latest complaint regarding the conduct of these two representatives would appear to have been generated out of temporal context as one of the representatives concerned was married in July and was now known by her married name. Thus a complaint made against her under her maiden name must have pre-dated the above events and the enforcing actions that Pasteur Mérieux MSD had taken in the meantime would have halted any such alleged activities.

The transcript was not a transcript of the actual proceedings of a "debate". The document was merely an outline of issues to be discussed in a light-hearted manner and was only intended for use by the participants in the "debate". This was only a very small part (less than 50 minutes) of an intensive 4 days of training on Avaxim. The debate was an amusing interlude during a highly technical training programme for the salesforce which took place in May 1996. Therefore this event predated all the correspondence from SmithKline Beecham on Avaxim since June and all the measures which Pasteur Mérieux MSD had taken to ensure that the salesforce stuck rigidly to the correct promotional messages.

The comments made in the document by "the judge" were greatly expanded on during the actual debate. The medical director clarified to the salesforce the rationale and technical background on the subject of interchangeability of hepatitis A vaccines. It was made clear during the proceedings that they must not promote outside the product licence.

The training manual was of an extremely high standard and the transcript did not form any part of this training package. This document was only intended for internal

use and not as part of the official briefing material and it was not necessary for it to be subject to internal approval procedures. The words were only an outline of comments made in the context of a light-hearted forum and, therefore, Pasteur Mérieux MSD did not accept that there had been a breach of Clause 8.1. Obviously the disputed comments were not for external use and they clearly contained nothing advocating actions to breach the Code. In view of the confidential internal nature of the document and its limited distribution, Pasteur Merieux MSD would be interested to learn the method by which SmithKline Beecham obtained a copy. The Authority might be interested to know that its clear company policy in such unethical breaches of confidence was immediately to return such documents to the company concerned.

With reference to SmithKline Beecham's claim that Pasteur Mérieux MSD was bringing the industry, as a whole, into disrepute, Pasteur Mérieux MSD strongly refuted this. As demonstrated above, it had made clear to the salesforce that promotion outside of the product licence was unacceptable. It rigorously investigated any complaints that might arise, thus maintaining the high standards demanded under the Code. It was not seeking competitive advantage by promoting claims for which it had no clinical evidence and it had made every effort to ensure that such claims were not made.

The Authority could see that there had been significant amounts of correspondence between the two companies, primarily generated by SmithKline Beecham. Pasteur Mérieux MSD's view was that undoubtedly this was prompted by SmithKline Beecham's sole intention by any means to protect its former monopoly position on the supply of hepatitis A vaccines to the UK market.

As a company with high ethical values, Pasteur Mérieux MSD continued to improve its own procedures and would once again review its standard operating procedures on copy approval to ensure that its exacting standards were maintained. It had also made arrangements for the whole of the salesforce to receive refresher training on the Code of Practice in addition to the training they already received for the ABPI examination.

However, it was always possible that, despite the rigorous training programme and the high quality training materials provided, Pasteur Mérieux MSD's message might have been misinterpreted by one or two of its sales representatives. Following letters from SmithKline Beecham, it would be seen that Pasteur Mérieux MSD had taken immediate and all necessary corrective action by re-instructing its salesforce, in case there was any misunderstanding.

Pasteur Mérieux MSD was at a loss to know why SmithKline Beecham considered it necessary to complain to the Authority at this time, when it had acted so promptly in response to SmithKline Beecham's written concerns over the last few months. It was concerned that the Authority had been asked to become involved in a matter as difficult as deciding on the validity of unsubstantiated claims and counter-claims from competing sales representatives.

**RULING**

The Panel considered that it would be difficult to be definitive as to whether Pasteur Mérieux MSD's representatives were making unacceptable claims at the present time. Any ruling would have to relate to past conduct. The case demonstrated the usual problem of knowing what occurred in contacts between doctors and representatives. The Panel noted that SmithKline Beecham had supplied the names of three practices which were willing to discuss the matter in confidence with the Authority but considered that it would be improper for it to do so as Pasteur Mérieux MSD would not be able to have the right of reply.

The Panel noted that the SPC for Avaxim stated that those who received Avaxim as primary immunisation should also have Avaxim as the booster. The fact that the SPC did not say that Avaxim could not be used as a booster to other hepatatis A vaccines did not mean, in the Panel's view, that it could be so promoted. Any promotion to that effect would be outside the terms of the marketing authorization. That point had been conceded by Pasteur Mérieux MSD.

The Panel did not consider that any breach of the Code was demonstrated by the letter to a practice which had been supplied by SmithKline Beecham. If, as appeared to be the case, it was a response to a specific enquiry about the matter then it was not unacceptable, as provided for in Clause 1.2 of the Code. It would, however, have been preferable for the letter to have been addressed to a specific doctor or doctors rather than to the surgery.

The transcript of the debate on "Havrix is the Gold Standard in Hepatitis A Prevention" was considered to be unacceptable. In the Panel's view it was training material and should have been certified. The statement that "It has been commented by experts that they do not believe using AVAXIM booster for Havrix primed patients should be a problem ( or vice versa)" positively encouraged Pasteur Mérieux MSD's representatives to use it as a claim, particularly as it was presumably part of the armaments referred to at the end of the transcript when it said "Go for it guys, we're sure with all this ammunition you will be able to handle anything and make a big close!". The transcript also made a number of disparaging comments about SmithKline Beecham and its activities. A breach of Clause 15.9 was ruled.

Having reviewed all of the correspondence, the Panel accepted that Pasteur Mérieux MSD representatives had claimed that Avaxim could be used as the booster dose for patients who had had primary immunisation with Havrix. It was not possible to determine the scale upon which the claim had been made or to what extent Pasteur Mérieux MSD had encouraged it but Pasteur Mérieux MSD was responsible for the activities of its representatives and they had clearly made this claim. Breaches of Clauses 3.2 and 15.2 were ruled.

The allegation of a breach of Clause 8.1 was considered to be covered by the Panel's ruling that the transcript was in breach of Clause 15.9. The reference to data becoming available soon was considered to be covered by the ruling of a breach of Clause 3.2. The matter was not considered to merit the particular censure of a ruling of a breach of Clause 2 or Clause 9.1.

**Complaint received** **7 October 1996**

**Case completed** **25 November 1996**

# CONSULTANT HAEMATOLOGIST v PHARMACIA & UPJOHN

## Focus Group on low molecular weight heparins

**Pharmacia & Upjohn organised an evening meeting to bring together a small, multidisciplinary group of health professionals to discuss the future marketing direction of low molecular weight heparins. A consultant haematologist complained that the size of the honorarium to attend the meeting was excessive.**

**The Panel noted that those attending the meeting were being invited to act as consultants to the company. The number of delegates was limited and this would ensure that all could make a contribution to the proceedings. The honorarium was not unreasonable for the amount of work involved and the hospitality was acceptable. No breach of the Code was ruled.**

A consultant haematologist complained about the arrangements for an evening meeting organised by Pharmacia & Upjohn. The meeting, to be held in a hotel, was entitled "Focus Group: The future direction of low molecular weight heparins in the UK". The meeting was to be comprised of a multidisciplinary group of about ten clinicians and pharmacists to discuss the likely future development of low molecular weight heparins from a marketing perspective. The purpose of the meeting was to obtain an up to date perspective regarding the current position of low molecular weight heparins and to establish a platform for their future marketing direction in the UK. The meeting was to last four hours. It started with coffee and drinks followed by a forty-five minute clinical overview on low molecular weight heparins from an independent physician. There was also a fifteen minute marketing presentation on Fragmin, Pharmacia & Upjohn's low molecular weight heparin. The rest of the time was to be spent in an interactive marketing workshop. A working dinner was to be served.

Pharmacia & Upjohn envisaged that the discussions would cover the current use of low molecular weight heparins in the UK, the future for low molecular weight heparins, the impact of patient centred care and issues in the development of new management strategies. A £200 honorarium and travel costs was to be paid.

### COMPLAINT

The complainant said that the honorarium of £200 to attend the meeting was excessive.

### RESPONSE

Pharmacia & Upjohn said that the objective of the meeting was to bring together a multidisciplinary group to discuss the future marketing direction of low molecular weight heparins in the UK.

The company had invited a guest speaker to present an overview of the current position of low molecular weight heparins in general in order that all participants would start the interactive marketing workshop with the same level of understanding of the current situation.

The main portion of the meeting would be taken up in attempting to determine the future direction of these products from a marketing perspective, with the participants being asked to work as marketers rather than clinicians.

Pharmacia & Upjohn submitted that the meeting had a clear educational content as expressed by the forty-five minute clinical overview. In addition the hospitality was secondary to the nature of the meeting, only a working buffet meal would be served. The meeting was non promotional; there was only a fifteen minute marketing overview in a meeting scheduled to last four hours. This overview would focus on the historical marketing development of the product, in order to assist in setting the scene for the interactive workshop.

With regard to the level of honoraria, Pharmacia & Upjohn submitted that in this instance it was asking the invited group to act as marketing consultants. The fee normally changed to the pharmaceutical industry for this type of consultation was approximately £80 per hour. Additionally, according to the BMA Fees Guidelines Schedule, the fee payable for participation in clinical trials was £121 per hour. Therefore an honoraria equating to approximately £50 per hour would not be seen to be excessive.

Pharmacia & Upjohn said that there would be no materials distributed at the meeting. The selection of possible members of the focus group was made on the basis of personal recommendation by representatives and managers, whose personal knowledge allowed the company to attempt to attract participants who were particularly interested in this area. Pharmacia & Upjohn confirmed that there was only one "Focus Group" meeting planned, attended by three company personnel.

### RULING

The Panel accepted that there was a difference between holding a meeting for health professionals and employing health professionals to act as consultants to a company.

The Panel noted that Pharmacia & Upjohn held only one "Focus Group" meeting and that the number of company personnel attending was modest. Although there was to be a presentation on the company's product Fragmin, this was to be short in comparison to the length of the whole meeting and the Panel considered that given the purpose of the meeting such a presentation was inevitable. The Panel considered that the arrangements for the meeting were such that all participants (approximately ten) could make a contribution to the proceedings.

The Panel was concerned that the delegates were identified by the sales force. Such a selection process could be open to criticism in that only good prescribers of Fragmin might be chosen or alternatively those who needed some persuasion to use the product. The delegates were being "employed" as consultants to the company and as such their inclusion in the "Focus Group" should stand up to independent scrutiny. The Panel considered

that the hospitality offered was not unreasonable.

The Panel had some concerns about the meeting as noted above but decided that on balance the payment of the £200 fee was a genuine payment for advice. It was not unreasonable for the amount of work involved. The Panel therefore ruled no breach of Clause 19.1 of the Code.

**Complaint received** **16 October 1996**

**Case completed** **18 December 1996**

---

**CASE AUTH/474/11/96**

# LOREX v YAMANOUCHI

## Labelling of Flomax MR samples

**Lorex alleged that a sample of Flomax MR which was labelled "Physician's Sample" failed to comply with the requirements of the Code.**

**The Panel did not accept Yamanouchi's contention that the pack was not a sample but a starter pack. The Code defined a starter pack as a small pack to provide sufficient medicine for a doctor to initiate treatment where there might be a delay in filling a prescription. The types of medicine for which starter packs were appropriate were limited. The pack did not comply with the requirement that samples be labelled "free medical sample - not for resale", or words to that effect, and a breach of the Code was ruled.**

### COMPLAINT

Lorex Synthélabo Limited complained about a sample of Flomax MR issued by Yamanouchi Pharma Ltd . Lorex Synthélabo said that this was labelled "Physician's Sample" which appeared to be in breach of Clause 17.5 of the Code. Lorex Synthélabo had asked Yamanouchi to rectify its labelling in accordance with the Code but to no avail.

### RESPONSE

Yamanouchi said that the Flomax MR packs in question were intended to provide starter packs to clinicians. Yamanouchi accepted that the use of the term "Physician's Sample" on the pack might perhaps have introduced some semantic confusion and perhaps might even have led Synthélabo to believe that this represented an opportunity to pursue a complaint.

Quite contrary to Lorex Synthélabo's assertion, Yamanouchi had in fact already taken action to amend the labelling of this particular pack, not because it believed that the pack constituted any possible breach of the Code, but in order to ensure that it did everything possible to overcome any possible doubt, confusion or uncertainty, and to emphasise its commitment to conforming to and upholding both the letter and the spirit of the Code.

The limited number of packs currently with its field force bore a non-removable type sticker saying "free medical sample not for resale". Future supplies of the pack would be printed with this text in place.

### RULING

The Panel noted that the supplementary information to Clause 17 stated that "Starter packs are small packs designed to provide sufficient medicine for a doctor to initiate treatment in such circumstances as a call out in the night or in other instances where there might be some undesirable but unavoidable delay in filling a prescription. It follows, therefore, that the types of medicines for which starter packs are appropriate are limited".

The Panel did not accept that Flomax MR, a treatment for the functional symptoms of benign prostatic hypertrophy, was a medicine for which a starter pack was appropriate. It did not need to be taken as an emergency measure.

In the Panel's view, the packs were samples and not starter packs as submitted by Yamanouchi. The labelling did not comply with the Code's requirement that samples be marked "free medical sample - not for resale", or words to that effect, and it was accordingly ruled that there had been a breach of Clause 17.5 of the Code.

**Complaint received** **13 November 1996**

**Case completed** **7 January 1997**

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

| | | | | |
|---|---|---|---|---|
| **433/5/96** | **Director/Media v Servier** | **Promotion of Coversyl** | **Breach 7.2** | **Appeal by respondent** |
| **446/7/96** | **Zeneca } v Orion** | **Promotion of Fareston** | **Breach 3.2, 4.1, 7.2, 7.7** | **} Appeal by } respondent** |
| **449/7/96** | **Hospital Doctor } v Orion** | | **7.2, 7.7** | **}** |
| **467/10/96** | **Hospital Doctor }** | | **7.2, 7.7** | **}** |
| **470/10/96** | **Director/Media }** | | **7.2, 7.7** | **}** |
| **452/8/96** | **Consultant Psychiatrist v Wyeth Lederle** | **"Psychiatry in Practice" journal** | **Breach 6.4, 9.9 & 10.1** | **Appeal by complainant** |
| **454/8/96** | **Norton Healthcare & )** | **Letter about Airomir** | **Breach 4.1, 7.2** | **Appeal by Glaxo Wellcome** |
| **459/8/96** | **Glaxo Wellcome ) v 3M Health Care )** | | | |
| **455/8/96** | **Searle v Boehringer Ingelheim** | **Mobic pre launch mailing and journal advertisement** | **Breach 7.2, 7.8** | **Appeal by respondent** |
| **463/9/96** | **Serono v Organon** | **"Orgyn" magazine** | **Breach 4.1,7.8 & 7.10** | **No appeal** |
| **466/10/96** | **University doctor v Boehringer Ingelheim** | **Mobic hospital detail aid** | **Breach 7.2 & 11.4** | **No appeal** |
| **468/10/96** | **SmithKline Beecham v Pasteur Mérieux MSD** | **Promotion of Avaxim** | **Breach 3.2, 15.2 & 15.9** | **No appeal** |
| 471/10/96 | Consultant haematologist v Pharmacia & Upjohn | Focus Group meeting | No Breach | No appeal |
| **474/11/96** | **Lorex v Yamanouchi** | **Labelling of Flomax samples** | **Breach 17.5** | **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).